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(54) **2-HYDROXYARYLAMIDE DERIVATIVE OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF, PREPARATION METHOD THEREOF, AND PHARMACEUTICAL COMPOSITION FOR PREVENTING OR TREATING CANCER CONTAINING SAME AS ACTIVE INGREDIENT**

(71) Applicant: **KOREA RESEARCH INSTITUTE OF BIOSCIENCE AND BIOTECHNOLOGY**, Daejeon (KR)

(72) Inventors: **Semi Kim**, Daejeon (KR); **Ill Young Lee**, Daejeon (KR); **Hye-Jin Min**, Daejeon (KR); **Eun-Hee Nam**, Daejeon (KR); **Pilho Kim**, Daejeon (KR); **Chang Soo Yun**, Daejeon (KR); **Dong Joon Ko**, Daejeon (KR)

(73) Assignee: **Korea Research Institute of Bioscience and Biotechnology** (KR)

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Related U.S. Application Data

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C07D 285/135	(2006.01)
C07D 213/75	(2006.01)
C07D 239/42	(2006.01)
C07D 277/46	(2006.01)
C07D 213/82	(2006.01)
C07D 215/56	(2006.01)
C07D 277/82	(2006.01)
A61K 31/4439	(2006.01)
A61K 31/428	(2006.01)
A61K 31/433	(2006.01)
A61K 31/44	(2006.01)
A61K 31/4709	(2006.01)
A61K 31/505	(2006.01)
A61K 31/5377	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 417/04*** (2013.01); ***A61K 31/167*** (2013.01); ***A61K 31/426*** (2013.01); ***A61K 31/428*** (2013.01); ***A61K 31/433*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/4439*** (2013.01); ***A61K 31/4709*** (2013.01); ***A61K 31/505*** (2013.01); ***A61K 31/5377*** (2013.01); ***C07D 213/75*** (2013.01); ***C07D 213/82*** (2013.01); ***C07D 215/38*** (2013.01); ***C07D 215/56*** (2013.01); ***C07D 239/42*** (2013.01); ***C07D 277/46*** (2013.01); ***C07D 277/82*** (2013.01); ***C07D 285/135*** (2013.01)

(58) **Field of Classification Search**

CPC . A61K 31/167; A61K 31/426; A61K 31/433; A61K 31/44; A61K 31/4709
USPC 514/313, 344, 363, 371, 617, 619
See application file for complete search history.

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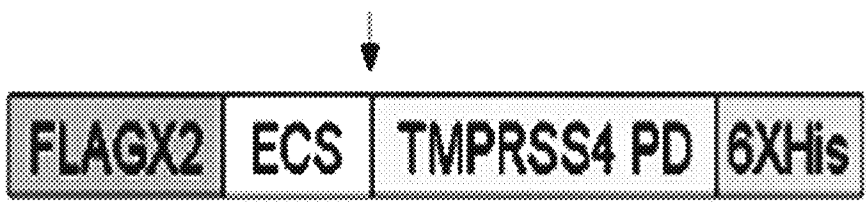
Primary Examiner — Deepak Rao
(74) *Attorney, Agent, or Firm* — Sheridan Ross P.C.

(57) **ABSTRACT**

The present invention relates to a 2-hydroxyarylamide derivative or a pharmaceutically acceptable salt thereof, a preparation method thereof, and a pharmaceutical composition for preventing or treating cancer comprising the same as an active ingredient. The 2-hydroxyarylamide derivative prepared by the present invention is excellent in the inhibition of the activity of TMPRSS4 serine protease and the suppression of the infiltration of TMPRSS4-expressed cancer cells, and thus can be useful as a composition for preventing or treating cancer by inhibiting TMPRSS4 over-expressed in cancer cells, particularly, colorectal cancer, lung cancer, breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, or stomach cancer cells.

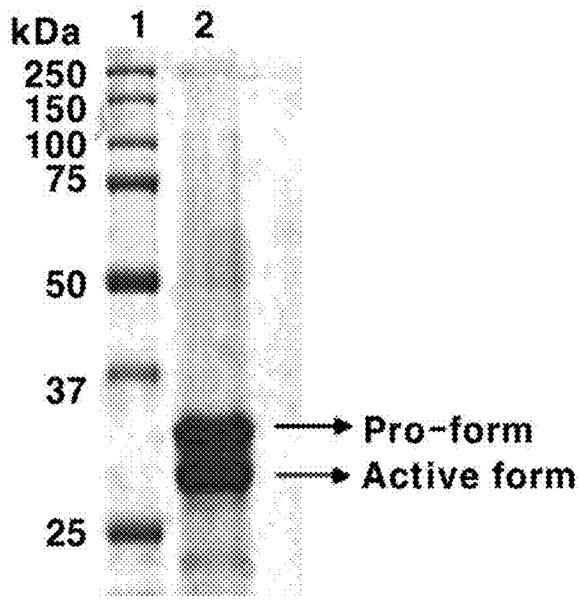
2 Claims, 4 Drawing Sheets

Fig 1



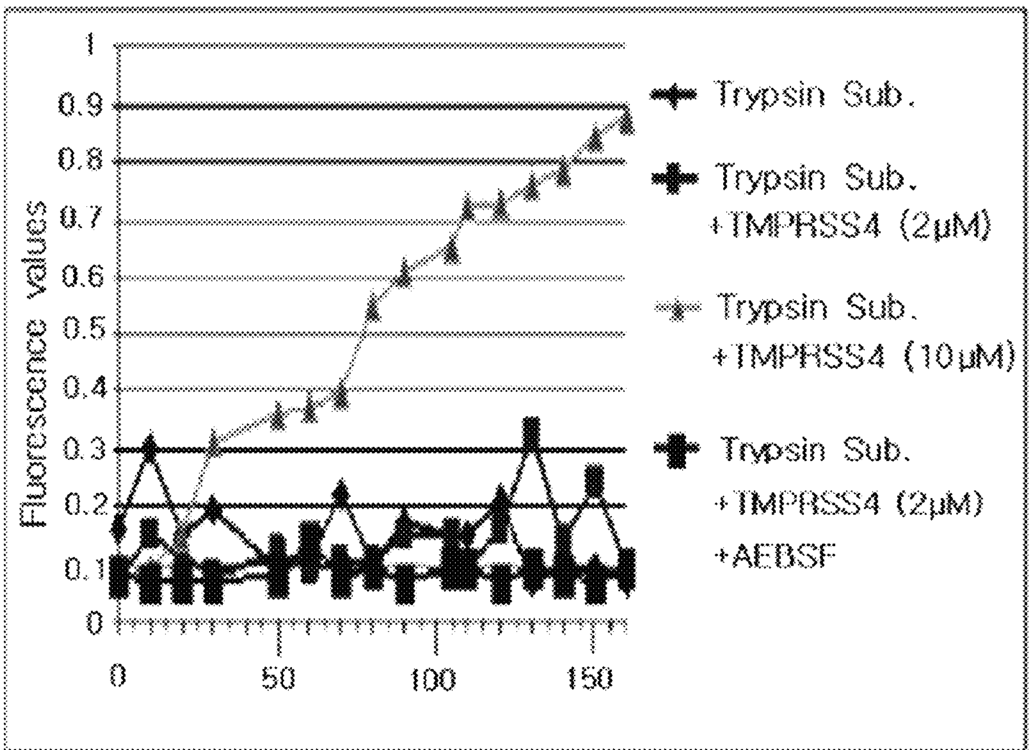
ECS: enterokinase cleavage site
TMPRSS4PD: TMPRSS4 protease domain (205Val..437Leu)

Fig 2



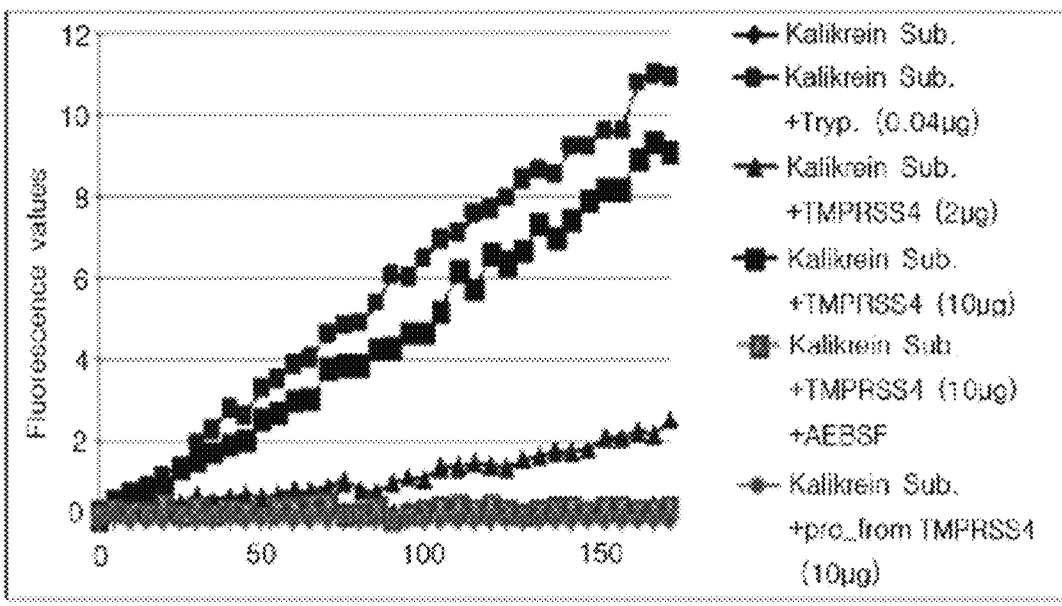
1:size marker
2:protease activated by enterokinase

Fig 3



Fluorescence values
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
50
100
150
Trypsin Sub.
Trypsin Sub.
+TMPRSS4 (2μM)
Trypsin Sub.
+TMPRSS4 (10μM)
Trypsin Sub.
+TMPRSS4 (2μM)
+AEBSF

Fig 4


12
10
8
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4
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Fluorescence values
0
50
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Kalikrein Sub.
Kalikrein Sub. +Tryp. (0.04μg)
Kalikrein Sub. +TMPRSS4 (2μg)
Kalikrein Sub. +TMPRSS4 (10μg)
Kalikrein Sub. +TMPRSS4 (10μg) +AEBSF
Kalikrein Sub. +pro_from TMPRSS4 (10μg)

2-HYDROXYARYLAMIDE DERIVATIVE OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF, PREPARATION METHOD THEREOF, AND PHARMACEUTICAL COMPOSITION FOR PREVENTING OR TREATING CANCER CONTAINING SAME AS ACTIVE INGREDIENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Continuation-in-Part of PCT Application No. PCT/KR2012/008626 having an international filing date of 19 Oct. 2012, which designated the United States, which PCT application claimed the benefit of Korean Patent Application No. 10-2011-0107934 filed Oct. 21, 2011, and Korean Patent Application No. 10-2012-0116733 filed 19 Oct. 2012, the disclosures of which are incorporated herein by reference.

REFERENCE TO SEQUENCE LISTING

This application contains a Sequence Listing submitted as an electronic text file named "14fpo_03_009_ST25.txt", having a size in bytes of 2 KB, and created on Apr. 18, 2014. The information contained in this electronic file is hereby incorporated by reference in its entirety pursuant to 37 CFR §1.52(e)(5).

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the method for treatment of cancer using 2-hydroxyarylamide derivative or a pharmaceutically acceptable salt thereof.

2. Description of the Related Art

In the clinical treatment of cancer patients, side effects accompanied particularly by chemo-therapy and radio-therapy are the major problem. So, it is an urgent request to develop an anticancer agent to reduce side effects accompanied by chemo-therapy. If only the gene products only expressed or specifically over-expressed in cancer cells are identified and if their expressions are inhibited without destroying cell differentiation or cell metabolism in normal cells, an anticancer agent that kills cancer cells specifically without destroying normal cells would be developed based on that. Thus, it is regarded as a promising method for the development of an anticancer agent having excellent therapeutic effect with less side effects to identify a protein expressed by an oncogene or a tumor suppressor gene inducing abnormal functioning of signal transduction pathway so as to convert the malfunctioning signal transduction pathway into normal functioning one.

In particular, the importance of a protease as a tumor and cancer related factor is increased day by day. Cell growth, angiogenesis, infiltration, migration, metastasis, survival, expansion, and progression of cancer cells are all mediated by signal transduction control system and proteolytic activities of various proteases. One of the most peculiar phenomenon is degradation and remodeling of extracellular matrix composing intercellular space matrix and basement membrane by unregulated protease. Cancer cells infiltrate into the neighboring tissues locally and far away by the said system. Infiltration and metastasis of cancer cells are clinically very important factors to determine the treatment prognosis of cancer patients.

Infiltration of cancer cells composed of three serial steps of adhesion, degradation of basement membrane, and migration is essential not only for metastasis but also for angiogenesis. For example in metastasis, cancer cell infiltration is inevitable process for cancer cells to migrate into blood stream or to other tissues through blood stream. Precisely, cancer cells are adhered on the adhesion molecule expressed on basement membrane and then induce the secretion of various proteases to decompose the basement membrane thereon, leading to the migration through the broken basement membrane. Marimastat, the inhibitor belonging to matrix metalloproteinase family, which is involved in the protein decomposition essential for cell infiltration, has been known to inhibit metastasis and angiogenesis as well by inhibiting cancer cell infiltration.

Therefore, protease can regulate cancer cell metastasis and those genes involved in the same can be used as cancer prognostic markers, suggesting that protease or those genes involved in the same are important targets of cancer treatment. The most representative metastasis related proteins are MMPs (matrix metalloproteinases), cathepsin B, cathepsin D, and serine protease including uPA (urokinase plasminogen activator) (non-patent reference 1). Among many proteases, TMPRSS4 has recently been identified in its biological functions to cancer (non-patent reference 2). According to the recent reports, TMPRSS4 is an important mediator for infiltration, metastasis, migration, and adhesion as well as EMP (epithelial mesenchymal transition) in human epithelial cancer cells. It has been pointed therefore that TMPRSS4 has a great potential as a target of cancer treatment. Nevertheless, studies on TMPRSS4 are not plenty enough. Considering the great potential of TMPRSS4 as a powerful and independent prognostic marker and as a target for the development of an inhibitor of infiltration and metastasis, it is also important to develop TMPRSS4 inhibitor as an anticancer target.

TMPRSS4 gene is also over-expressed in malignant thyroid neoplasms. Therefore, The gene is proposed as a diagnostic and prognostic marker in such types of cancer (non-patent references 3 and 4).

Up to date, various compositions for treating cancer have been studied, which have been mainly focused on the inhibition of cancer specific marker. However, the studies on TMPRSS4 considered as a target of cancer treatment have not been actively undergoing.

The present inventors have studied to develop an anticancer agent to inhibit metastasis by suppressing cancer cell infiltration by inhibiting TMPRSS4 over-expressed specifically in cancer cells. In the course of the study, the inventors prepared a 2-hydroxyarylamide derivative and confirmed that the compound had excellent effect of inhibiting TMPRSS4, leading to the completion of this invention.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a 2-hydroxyayrlamide derivative or a pharmaceutically acceptable salt thereof.

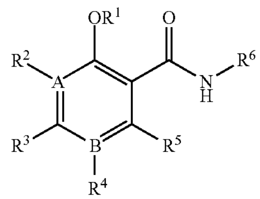
It is another object of the present invention to provide a preparation method of the 2-hydroxyarylamide derivative.

It is also an object of the present invention to provide a pharmaceutical composition for preventing or treating cancer which comprises the 2-hydroxyarylamide derivative or the pharmaceutically acceptable salt thereof as an active ingredient.

It is further an object of the present invention to provide a pharmaceutical composition for inhibiting TMPRSS4 (transmembrane protease serine-4) which comprises the 2-hydroxyarylamide derivative or the pharmaceutically acceptable salt thereof as an active ingredient.

To achieve the above objects, the present invention provides a 2-hydroxyarylamide derivative represented by the below Formula 1 or a pharmaceutically acceptable salt thereof:

[Formula 1]



(R^1~R^6, A and B are as defined in this description).

Further, the present invention provides a preparation method of the 2-hydroxyarylamide derivative represented by the above Formula 1.

The present invention also provides a pharmaceutical composition for preventing or treating cancer which comprises the 2-hydroxyarylamide derivative represented by the above Formula 1 or the pharmaceutically acceptable salt thereof as an active ingredient.

In addition, the present invention provides a pharmaceutical composition for inhibiting TMPRSS4 (transmembrane protease serine-4) which comprises the 2-hydroxyarylamide derivative represented by the above Formula 1 or the pharmaceutically acceptable salt thereof as an active ingredient.

Advantageous Effect

As explained hereinbefore, the 2-hydroxyarylamide derivative compound prepared in this invention has the effect of inhibiting the activity of TMPRSS4 serine protease and suppressing the infiltration of cancer cells expressing TMPRSS4, so that it can be useful as a composition for preventing or treating cancer by inhibiting TMPRSS4 overexpressed in cancer cells, particularly, colorectal cancer, lung cancer, breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, or stomach cancer cells.

BRIEF DESCRIPTION OF THE DRAWINGS

The application of the preferred embodiments of the present invention is best understood with reference to the accompanying drawings, wherein:

FIG. **1** is a diagram illustrating the cleavage site of FlagX2-enterokinase inserted in N-terminal of TMPRSS4 serine protease domain of Experimental Example 1.

FIG. **2** is a diagram illustrating the effect of the treatment of enterokinase after the expression/purification of protein from *E. coli* of Experimental Example 1.

FIG. **3** is a diagram illustrating the activity against trypsin peptide matrix of Experimental Example 1.

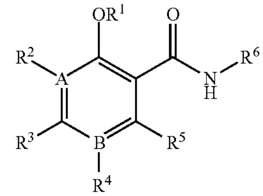
FIG. **4** is a diagram illustrating the activity against kallikrein peptide matrix of Experimental Example 1.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Hereinafter, the present invention is described in detail.

The present invention provides a 2-hydroxyarylamide derivative represented by the below Formula 1 or a pharmaceutically acceptable salt thereof.

[Formula 1]



In Formula 1,

R^1 is hydrogen, C_1-C_6 straight or branched alkylcarbonyl or benzyl,

R^2, R^3, R^4, and R^5 are independently hydrogen, halogen, C_1-C_6 straight or branched alkyl, C_1-C_6 straight or branched alkoxy, C_1-C_6 straight or branched haloalkyl, nitro, cyano, hydroxy, amino, aminocarbonyl, C_1-C_6 straight or branched alkylcarbonylamino, and C_5-C_7 aryl substituted with one or more halogens,

R^2 and R^3 can form C_5-C_7 aryl or heteroaryl along with atoms which are conjugated to the same,

R^6 is unsubstituted C_5-C_7 aryl or C_5-C_7 aryl substituted with one or more compounds selected from the group consisting of halogen, C_1-C_6 straight or branched alkyl, C_1-C_6 straight or branched alkoxy, C_1-C_6 straight or branched haloalkyl, cyano, amino, and nitro; or C_5-C_{12} monocyclic or bicyclic heteroaryl substituted with one or more compounds selected from the group consisting of halogen, C_1-C_6 straight or branched alkyl, C_1-C_6 straight or branched haloalkyl, and C_5-C_7 aryl. At this time, the said heteroaryl can include one or more hetero atoms selected from the group consisting of N, P, and S, and

A and B are independently carbon (C) or nitrogen (N), and at this time both A and B can not be nitrogen at the same time.

Preferably,

R^1 is hydrogen, C_1-C_4 straight or branched alkylcarbonyl or benzyl,

R^2, R^3, R^4, and R^5 are independently hydrogen, halogen, C_1-C_4 straight or branched alkyl, C_1-C_4 straight or branched alkoxy, C_1-C_4 straight or branched haloalkyl, nitro, cyano, hydroxy, amino, aminocarbonyl, C_1-C_4 straight or branched alkylcarbonylamino, and phenyl substituted with one or more halogens,

R^2 and R^3 can form C_5-C_7 aryl along with atoms which are conjugated to the same,

R^6 is unsubstituted phenyl or phenyl substituted with one or more compounds selected from the group consisting of halogen, C_1-C_4 straight or branched alkyl, C_1-C_4 straight or branched alkoxy, C_1-C_4 straight or branched haloalkyl, cyano, amino, and nitro; or pyridine, pyrimidine, thiazole, thiadiazole or isoquinoline substituted with one or more compounds selected from the group consisting of halogen, C_1-C_4 straight or branched alkyl, C_1-C_4 straight or branched haloalkyl, and C_5-C_7 aryl, and

A and B are independently carbon (C) or nitrogen (N), and at this time both A and B can not be nitrogen at the same time.

More preferably,

R^1 is hydrogen, acetyl or benzyl,

R^2 is hydrogen, halogen, methyl or ethyl,

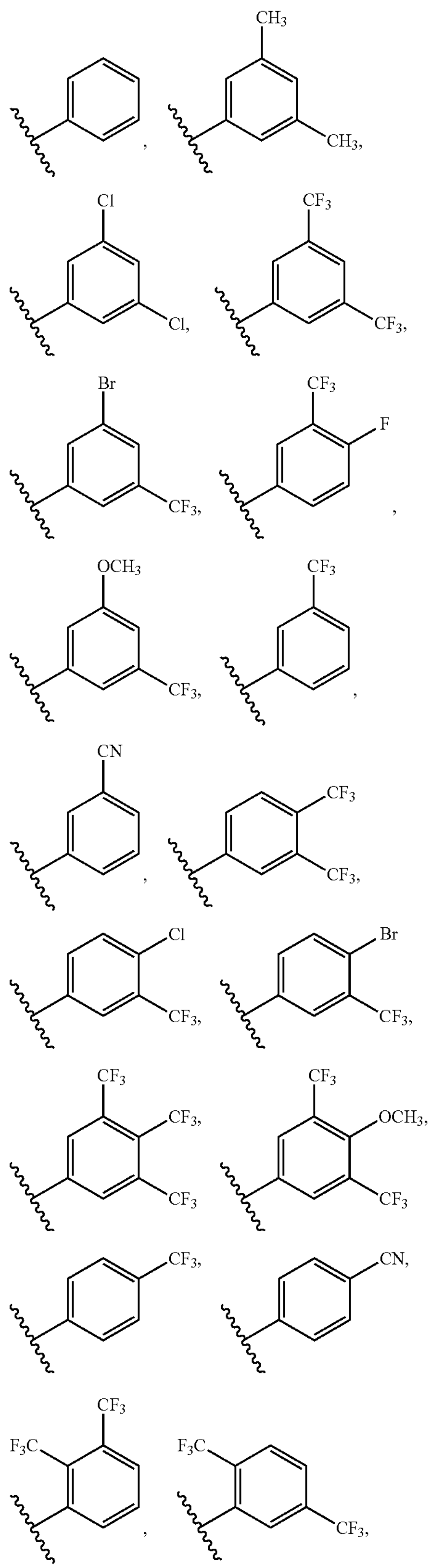
R^3 is hydrogen, halogen or trifluoromethyl,

R^2 and R^3 can form phenyl along with atoms which are conjugated to the same,

R^4 is a compound selected from the group consisting of hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, nitro, cyano, amino, methylcarbonylamino, aminocarbonyl and 2,4-difluorophenyl,

R^5 is hydrogen,

R^6 is a compound selected from the group consisting of



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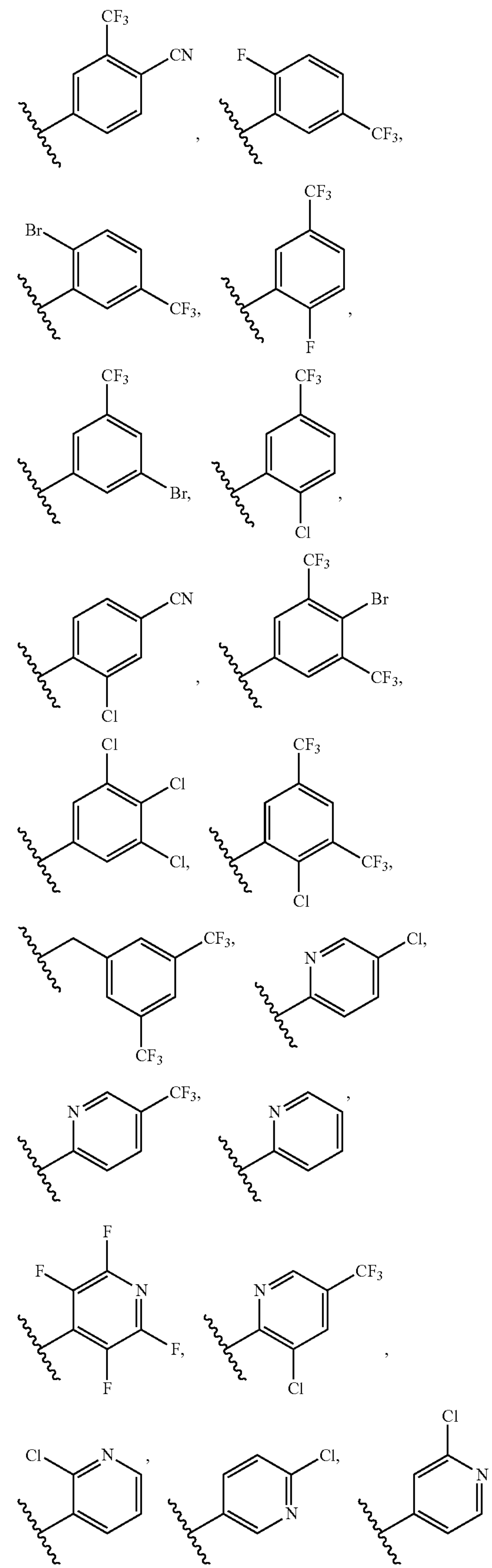

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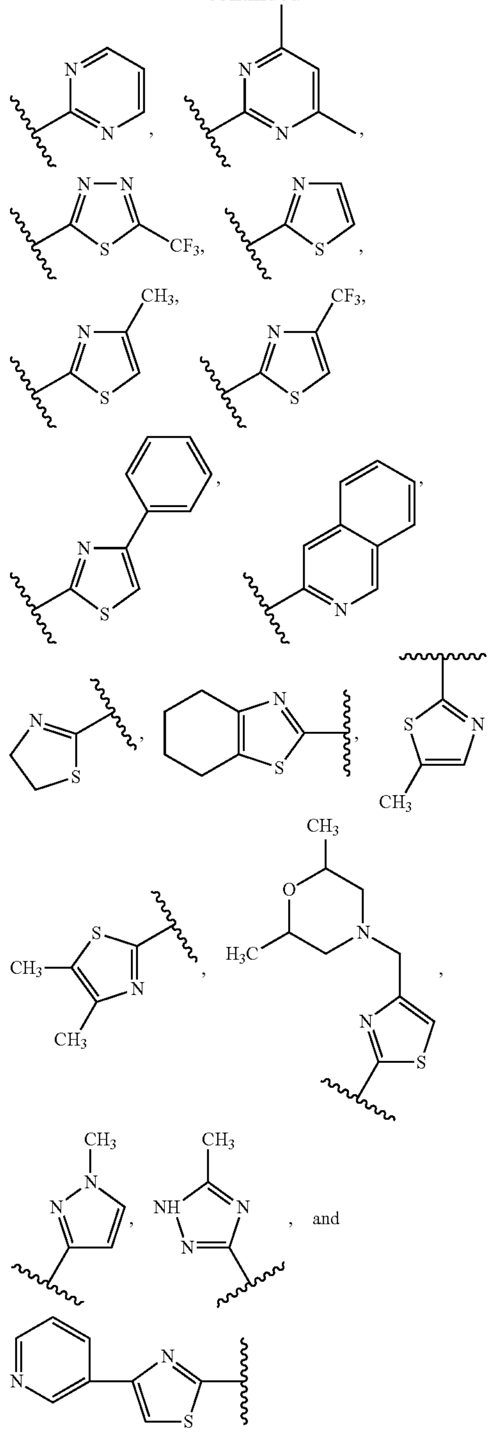


and

A and B are independently carbon (C) or nitrogen (N), and at this time both A and B can not be nitrogen at the same time.

The 2-hydroxyarylamide derivative represented by Formula 1 is more specifically exemplified by followings:

(1) N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide;

(2) N-(3,5-bis(trifluoromethyl)phenyl)3,5-dichloro-2-hydroxybenzamide;

(3) N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-methylbenzamide;

(4) 5-chloro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(5) N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(6) 5-chloro-2-hydroxy-N-(3-methoxy-5-(trifluoromethyl)phenyl)benzamide;

(7) N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-methoxybenzamide;

(8) N-(3,5-bis(trifluoromethyl)phenyl)-3-hydroxy-2-naphthaamide;

(9) N-(3,5-bis(trifluoromethyl)phenyl)-5-bromo-2-hydroxybenzamide;

(10) 5-chloro-N-(3-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(11) 5-chloro-N-(3-cyanophenyl)-2-hydroxybenzamide;

(12) 5-chloro-N-(4-cyanophenyl)-2-hydroxybenzamide;

(13) N-(3,5-bis(trifluoromethyl)phenyl)-4-(trifluoromethyl)-2-hydroxybenzamide;

(14) N-(3,5-bis(trifluoromethyl)phenyl)-5-fluoro-2-hydroxybenzamide;

(15) 5-chloro-N-(4-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(16) N-(4-bromo-3-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamine;

(17) 5-chloro-N-(3-(trifluoromethyl)-2-methylphenyl)-2-hydroxybenzamide;

(18) N-(2,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamine;

(19) 5-chloro-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(20) N-(2-bromo-5-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide;

(21) 5-chloro-N-(2-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(22) N-(3-bromo-5-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide;

(23) 5-chloro-N-(2-chloro-5-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(24) N-(3,5-bis-trifluoromethyl-benzyl)-5-chloro-2-hydroxy-benzamide;

(25) 5-chloro-2-hydroxy-N-quinoline-3-yl-benzamide;

(26) N-(3,5-bis-trifluoromethyl-phenyl)-3-chloro-2-hydroxy-benzamide;

(27) 5-chloro-N-(2-chloro-4-cyano-phenyl)-2-hydroxy-benzamide;

(28) 5-chloro-2-hydroxy-N-(5-trifluoromethyl-[1,3,4]thiadiazole-2-yl)-benzamide;

(29) 5-chloro-N-(2-chloro-3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-benzamide;

(30) N-(2-chloro-3,5-bis(trifluoromethyl)phenyl)-4',6'-difluoro-4-hydroxybiphenyl-3-carboxyamide;

(31) 5-amino-N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(32) 5-chloro-N-(4-chloro-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(33) 5-chloro-2-hydroxy-N-(4-methyl-3,5-bis(trifluoromethyl)phenyl)benzamide;

(34) N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxy-3-methylbenzamide;

(35) 5-acetoamido-N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(36) 5-chloro-2-hydroxy-N-(2-nitro-4-trifluoromethyl-phenyl)-benzamide;

(37) 5-chloro-N-(5-cyano-pyridine-2-yl)-2-hydroxy-benzamide;

(38) N3-(3,5-bis-trifluoromethyl-phenyl)-4-hydroxy-isophthalamide;

(39) 5-chloro-2-hydroxy-N-(4-methoxy-3,5-bis-trifluoromethyl-phenyl)-benzamide;

(40) 5-chloro-2-hydroxy-N-(pyridine-2-yl)benzamide;

(41) 5-chloro-2-hydroxy-N-(5-(trifluoromethyl)pyridine-2-yl)benzamide;

(42) 5-chloro-N-(5-chloropyridine-2-yl)-2-hydroxybenzamide;

(43) 5-chloro-2-hydroxy-N-(perfluoropyridine-4-yl)benzamide;

(44) 5-chloro-N-(2-chloropyridine-3-yl)-2-hydroxybenzamide;

(45) 5-chloro-N-(6-chloropyridine-3-yl)-2-hydroxybenzamide;

(46) 5-chloro-N-(3-chloro-5-(trifluoromethyl)pyridine-2-yl)-2-hydroxybenzamide;

(47) 5-chloro-N-(2-chloropyridine-4-yl)-2-hydroxybenzamide;

(48) 5-chloro-N-(4,6-dimethylpyrimidine-2-yl)-2-hydroxybenzamide;

(49) 5-chloro-2-hydroxy-N-(pyrimidine-2-yl)benzamide;

(50) 5-chloro-2-hydroxy-N-(4-methylthiazole-2-yl)benzamide;

(51) 5-chloro-2-hydroxy-N-(thiazole-2-yl)benzamide;

(52) 5-chloro-2-hydroxy-N-(4-(trifluoromethyl)thiazole-2-yl)benzamide;

(53) 5-chloro-2-hydroxy-N-(4-phenylthiazole-2-yl)benzamide;

(54) N-(3,5-bis(trifluoromethyl)phenyl)-4-chloro-2-hydroxybenzamide;

(55) N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-nitrobenzamide;

(56) N-(3,5-bis(trifluoromethyl)phenyl)-5-cyano-2-hydroxybenzamide;

(57) 2-(3,5-bis(trifluoromethyl)phenylcarbamoyl)-4-chlorophenylacetate;

(58) 2-benzyloxy-N-(3,5-bis-trifluoromethyl-phenyl)-5-chlorobenzamide;

(59) 5-chloro-2-hydroxy-N-phenylbenzamide;

(60) 5-chloro-N-(3,5-dimethylphenyl)-2-hydroxybenzamide;

(61) 5-chloro-N-(3,5-dichlorophenyl)-2-hydroxybenzamide;

(62) N-(3,4-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide;

(63) N-(4-bromo-3-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide;

(64) 5-chloro-N-(2-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(65) N-(4-bromo-3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide;

(66) 5-chloro-2-hydroxy-N-(3,4,5-trichloro-phenyl)benzamide;

(67) N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxynicotineamide;

(68) N-(3,5-bis(trifluoromethyl)phenyl)-4-hydroxyquinoline-3-carboxyamide;

(69) 5-chloro-N-(4,5-dihydrothiazol-2-yl)-2-hydroxybenzamide;

(70) 5-chloro-2-hydroxy-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

(71) 5-chloro-2-hydroxy-N-(5-methylthiazole-2-yl)benzamide;

(72) 5-chloro-N-(4,5-dimethylthiazol-2-yl)-2-hydroxybenzamide;

(73) 5-chloro-N-(4-((2,6-dimethylmorpholino)methyl)thiazol-2-yl)-2-hydroxybenzamide;

(74) 5-chloro-2-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

(75) 5-chloro-2-hydroxy-N-(5-methyl-1H-1,2,4-triazol-3-yl)benzamide; and

(76) 5-chloro-2-hydroxy-N-(4-(pyridin-3-yl)thiazol-2-yl)benzamide.

The preferable structure of the 2-hydroxyarylamide derivative represented by Formula of the present invention is presented in Table 1.

TABLE 1

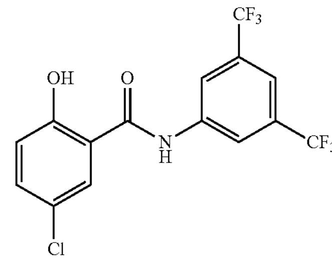
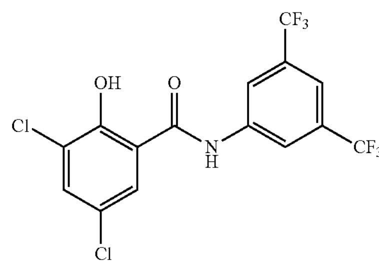
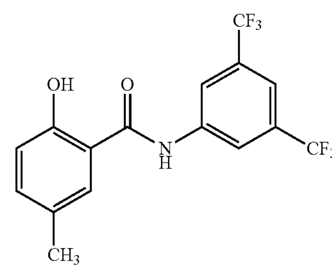
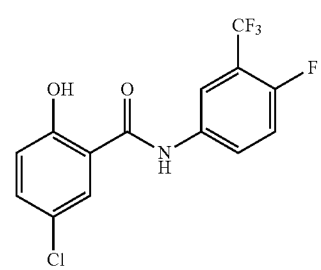
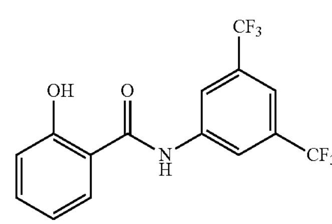
No.	Structural Formula
1	
2	
3	
4	
5	

TABLE 1-continued

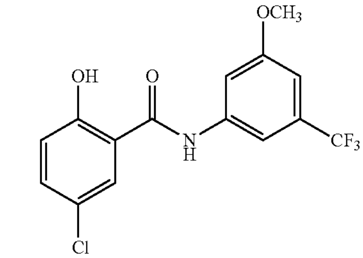
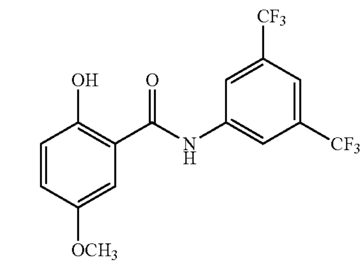
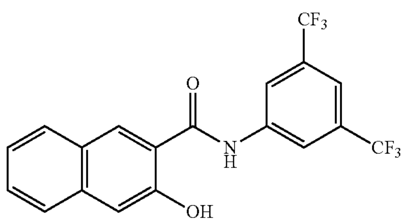
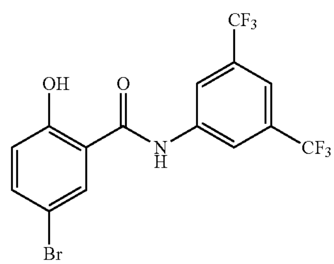
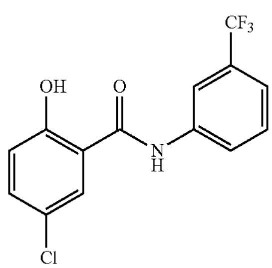
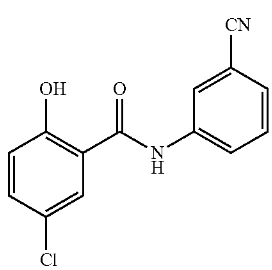
No.	Structural Formula
6	
7	
8	
9	
10	
11	

TABLE 1-continued

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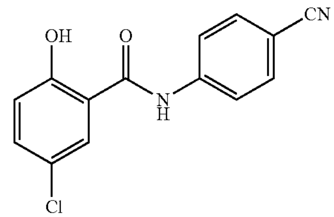
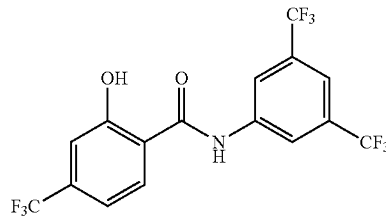
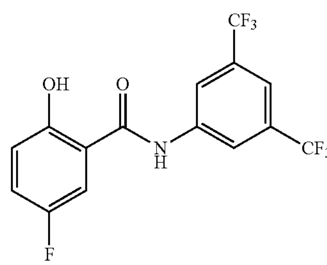
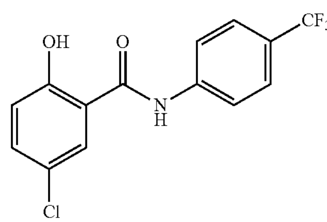
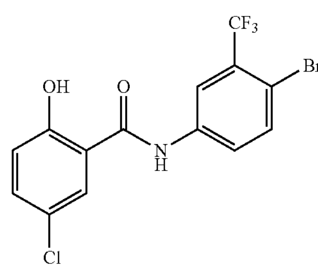
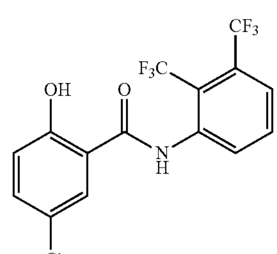
12	
13	
14	
15	
16	
17	

TABLE 1-continued

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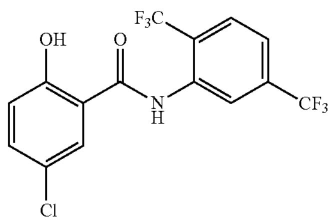
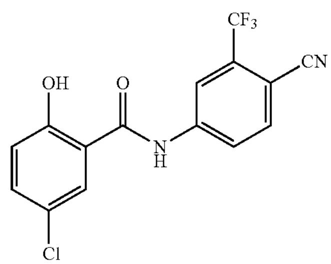
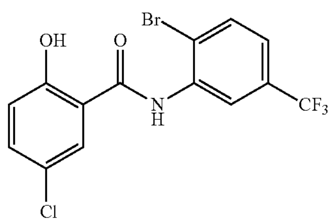
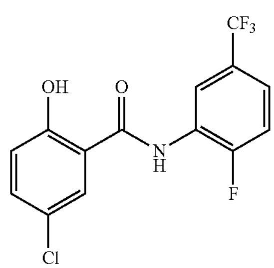
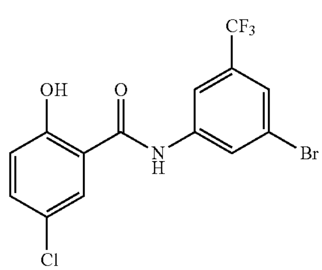
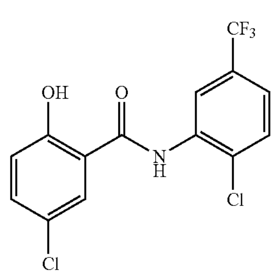
18	
19	
20	
21	
22	
23	

TABLE 1-continued

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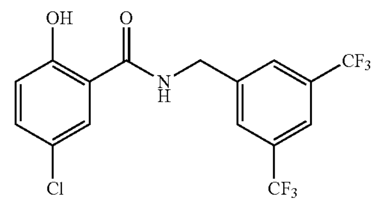
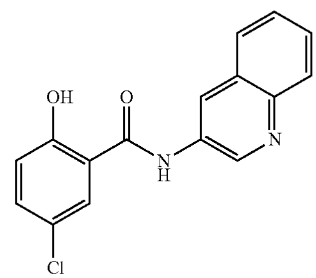
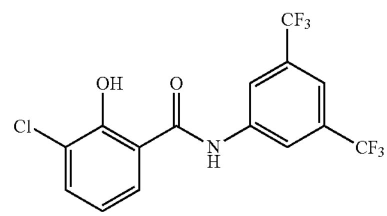
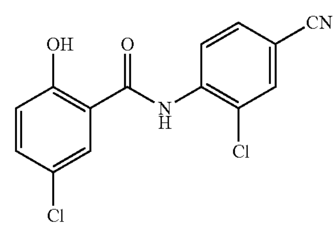
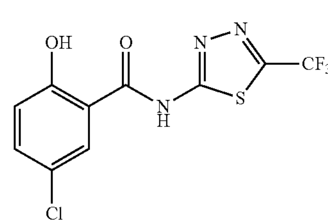
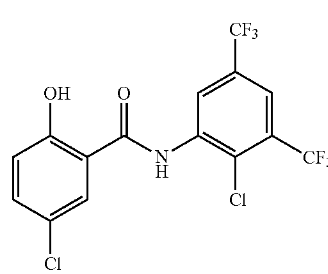
24	
25	
26	
27	
28	
29	

TABLE 1-continued

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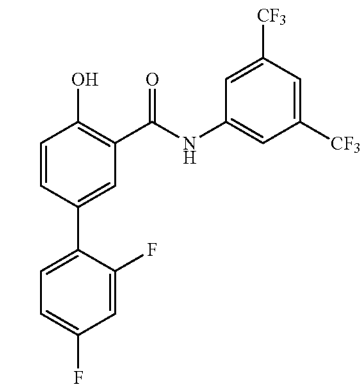
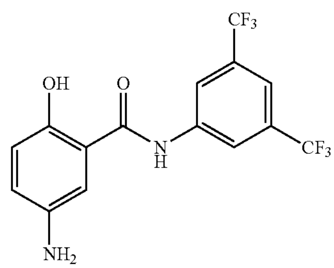
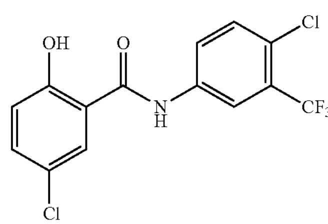
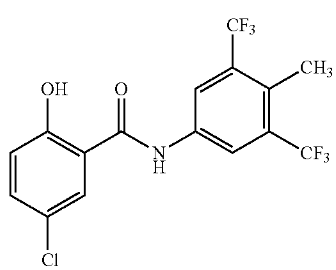
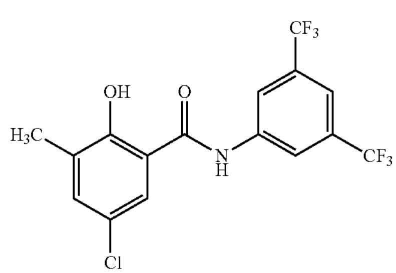
30	
31	
32	
33	
34	

TABLE 1-continued

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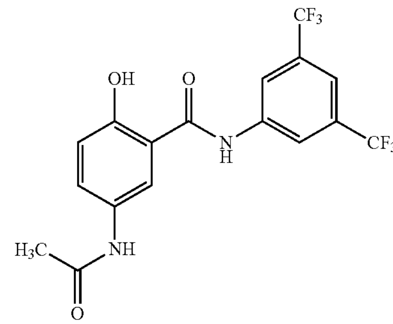
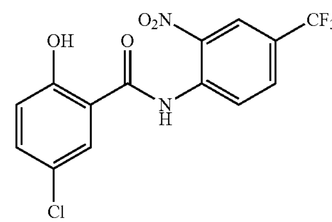
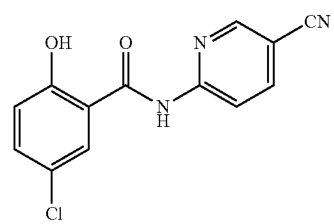
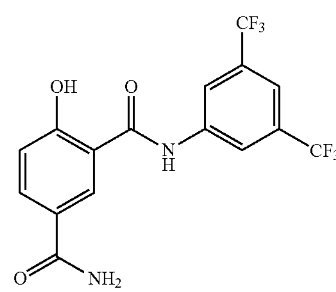
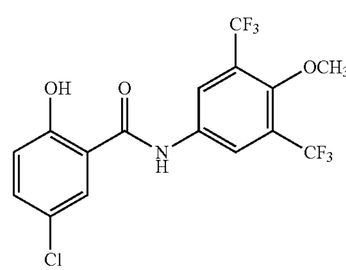
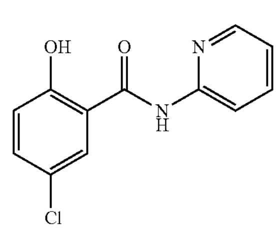
35	
36	
37	
38	
39	
40	

TABLE 1-continued

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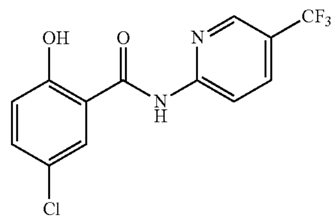
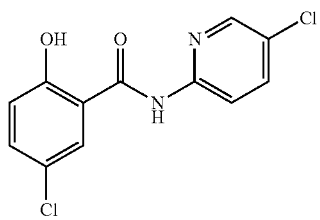
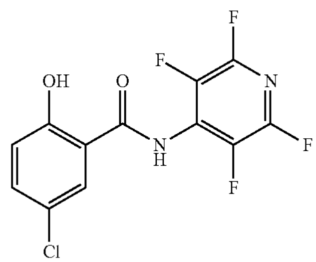
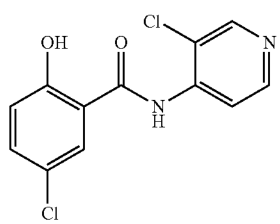
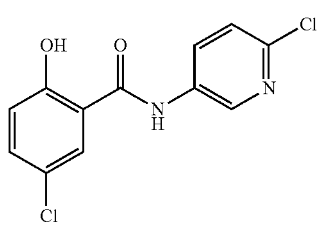
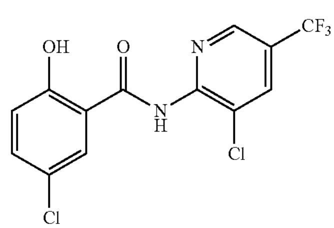
41	
42	
43	
44	
45	
46	

TABLE 1-continued

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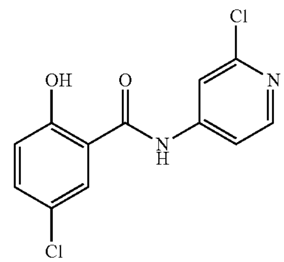
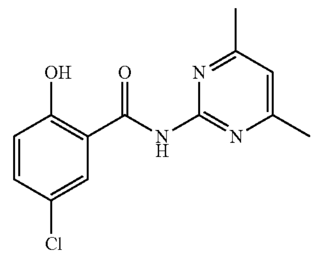
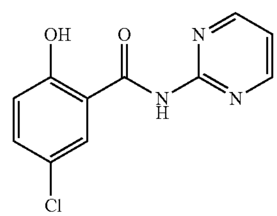
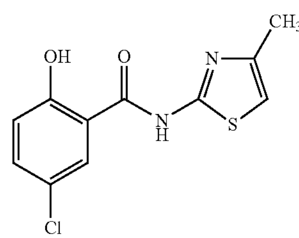
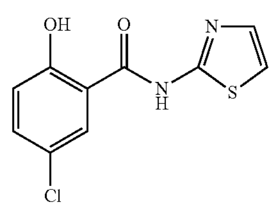
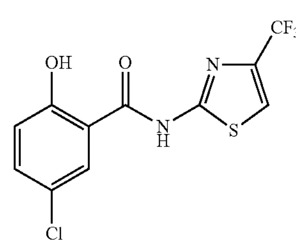
47	
48	
49	
50	
51	
52	

TABLE 1-continued

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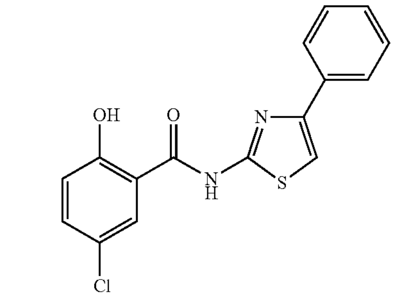
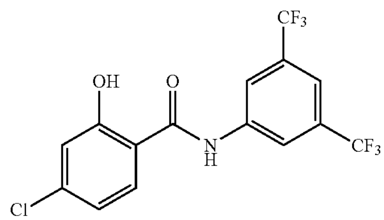
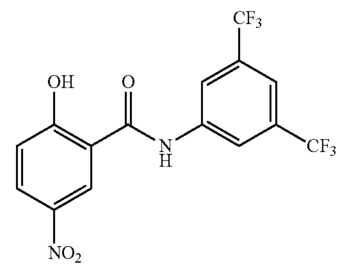
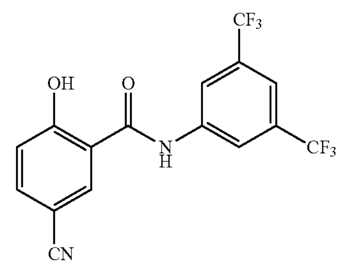
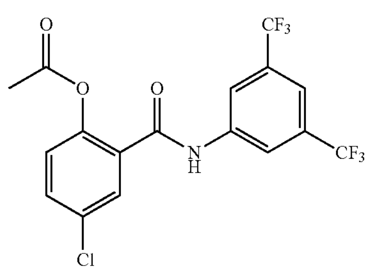
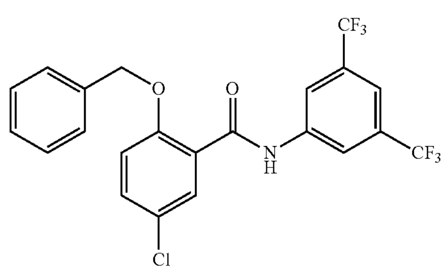
53	
54	
55	
56	
57	
58	

TABLE 1-continued

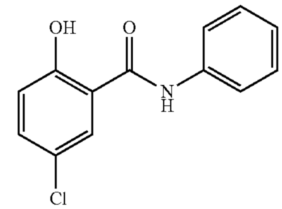
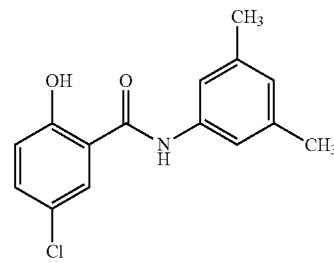
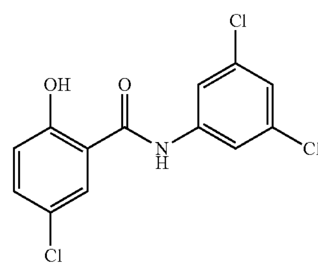
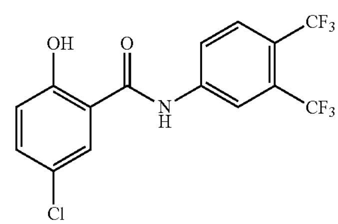
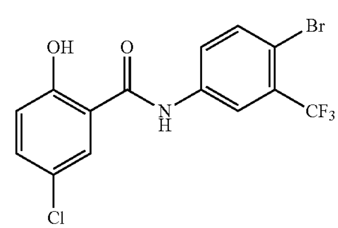
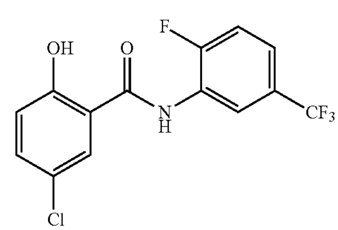
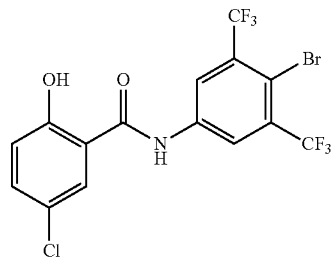
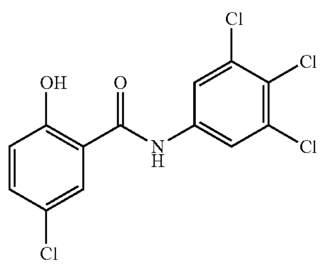
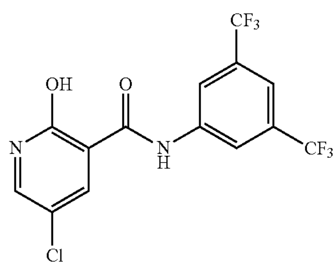
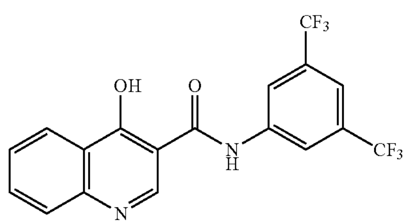
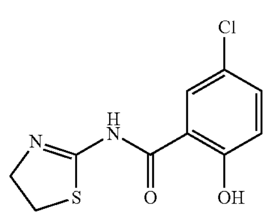
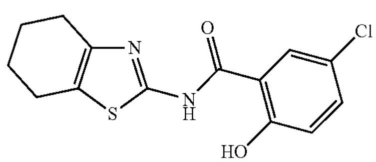
No.	Structural Formula
59	
60	
61	
62	
63	
64	

TABLE 1-continued

No.	Structural Formula
65	
66	
67	
68	
69	
70	

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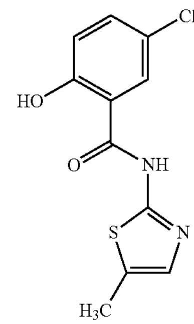
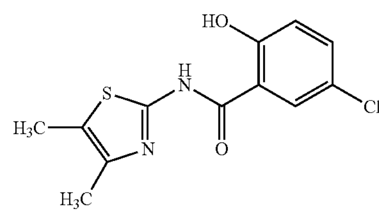
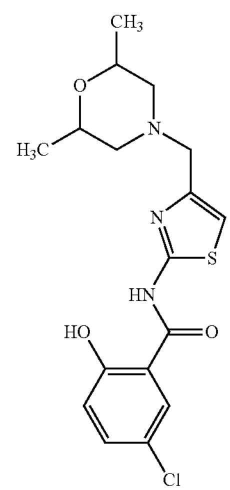
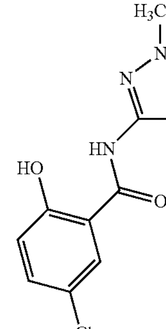
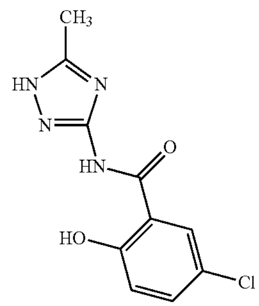
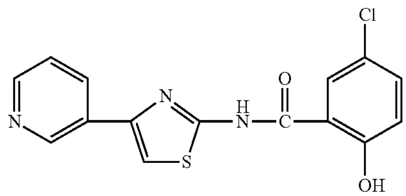
71	
72	
73	
74	

TABLE 1-continued

No.	Structural Formula
75	
76	

The derivative of Formula 1 of the present invention can be used as a form of a pharmaceutically acceptable salt, in which the salt is preferably acid addition salt formed by pharmaceutically acceptable free acids. The acid addition salt herein can be obtained from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, nitrous acid, or phosphorous acid; or non-toxic organic acids such as aliphatic mono/di-carboxylate, phenyl-substituted alkanoate, hydroxy alkanoate/alkanedioate, aromatic acids, aliphatic and aromatic sulfonic acids. The pharmaceutically non-toxic salt is exemplified by sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate chloride, bromide, iodide, fluoride, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutylate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maliate, butin-1,4-dioate, hexane-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitro benzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutylate, citrate, lactate, β-hydroxybutylate, glycolate, malate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, or mandelate.

The acid addition salt in this invention can be prepared by the conventional method known to those in the art. For example, the derivative of Formula 1 of the present invention is dissolved in an organic solvent such as methanol, ethanol, acetone, methylenechloride, and acetonitrile, followed by adding organic acid or inorganic acid. The obtained precipitate is filtered, and then dried to give acid addition salt. Or the precipitate is vacuum-distillated with a solvent and excessive acid, followed by drying or crystallization in an organic solvent to give acid addition salt.

A pharmaceutically acceptable metal salt can be prepared by using a base. Alkali metal or alkali earth metal salt is obtained by the following processes: dissolving the compound in excessive alkali metal hydroxide or alkali earth metal hydroxide solution; filtering non-soluble compound salt; evaporating the remaining solution and drying thereof. At this time, the metal salt is preferably prepared in the pharmaceutically suitable form of sodium, potassium, or calcium salt. And the corresponding silver salt is prepared by the reaction of alkali metal or alkali earth metal salt with proper silver salt (ex; silver nitrate).

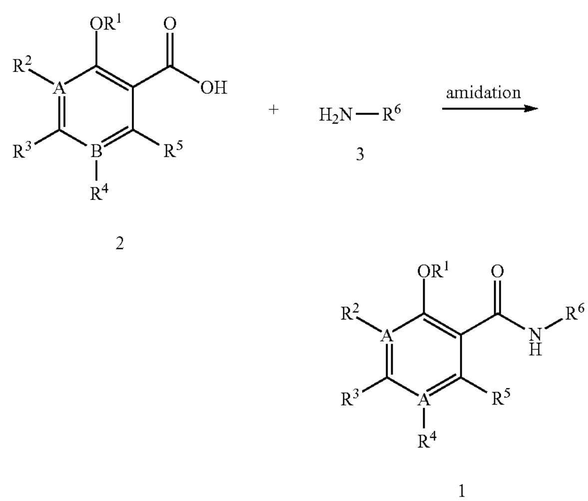
The present invention not only includes the 2-hydroxyarylamide derivative represented by Formula 1 but also includes the pharmaceutically acceptable salts thereof, every possible solvates, and hydrates constructed from the same.

In addition, the present invention provides a preparation method of the 2-hydroxyarylamide derivative represented by Formula 1.

Preparation Method 1

The preparation method of the derivative represented by Formula 1 of the present invention includes the step of preparing the compound of Formula 1 through amidation with the 2-hydroxyaryl acid compound represented by Formula 2 and the amine compound represented by Formula 3:

[Reaction Formula 1]



(In Reaction Formula 1, R^1~R^6, A and B are as defined in Formula 1).

In the preparation method 1 of the present invention, the 2-hydroxyarylamide derivative represented by Formula 1 is prepared as follows: the 2-hydroxyaryl acid compound represented by Formula 2 and an amide synthesis reagent are dissolved in an organic solvent; the amine compound represented by Formula 3 is added thereto; and the mixture is stirred to give the 2-hydroxyarylamide derivative represented by Formula 1.

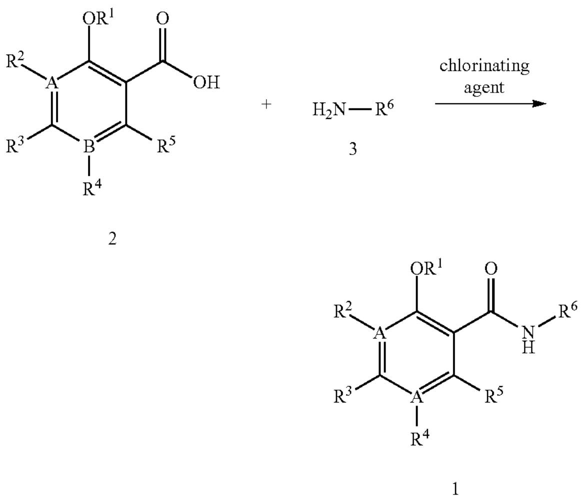
The said amide reagent can be diisopropylethylamine, triethylamine, dimethylaminopyridine (DMAP), benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphoniumhexafluorophosphate (Py-BOP), O-benzotriazole-N,N,N,N-tetramethyl-uronium-hexafluoro-phosphate (HBTU), 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HATU), hydroxybenzotriazole (HOBt), dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), or carbonyldiimidazole (CDI), and preferably hydroxybenzotriazole (HOBt) and/or O-benzotriazole-N,N,N,N-tetramethyl-uronium-hexafluoro-phosphate (HBTU).

The usable organic solvent herein is selected from the group consisting of methanol, dimethylformamide, tetrahydrofurane, dichloromethane, and toluene, which have no effect on the reaction, and preferably is dichloromethane.

Preparation Method 2

The preparation method of the derivative represented by Formula 1 of the present invention includes the step of preparing the compound of Formula 1 through coupling reaction with the 2-hydroxyaryl acid compound represented by Formula 2 and the amine compound represented by Formula 3 using a chlorinating agent:

[Reaction Formula 2]



(In Reaction Formula 2, R^1~R^6, A and B are as defined in Formula 1).

In the preparation method 2 of the present invention, the 2-hydroxyarylamide derivative represented by Formula 1 is prepared as follows: the 2-hydroxyaryl acid compound represented by Formula 2 is dissolved in an organic solvent in the presence of argon gas; a chlorinating agent is added thereto in the presence of a base; the amine compound represented by Formula 3 is added thereto; and the mixture is reflux-stirred to give the 2-hydroxyarylamide derivative represented by Formula 1.

The said chlorinating agent is selected from the group consisting of PCl_3, $POCl_3$, $SOCl_2$, SO_2Cl_2, and $COCl_2$, and is preferably PCl_3.

The base herein is selected from the group consisting of methylamine, ethylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, cyclohexylamine, diethylisopropylamine, and pyridine, and is preferably pyridine or triethylamine, but not always limited thereto.

The usable organic solvent herein can be dichloromethane, chloroform, tetrahydrofurane, diethylether, toluene, xylene, benzene, chlorobenzene, or dimethylformamide, which has no effect on the reaction, and is preferably toluene.

The reaction temperature is not limited to a specific range, but the range from room temperature to boiling point of a solvent is preferred.

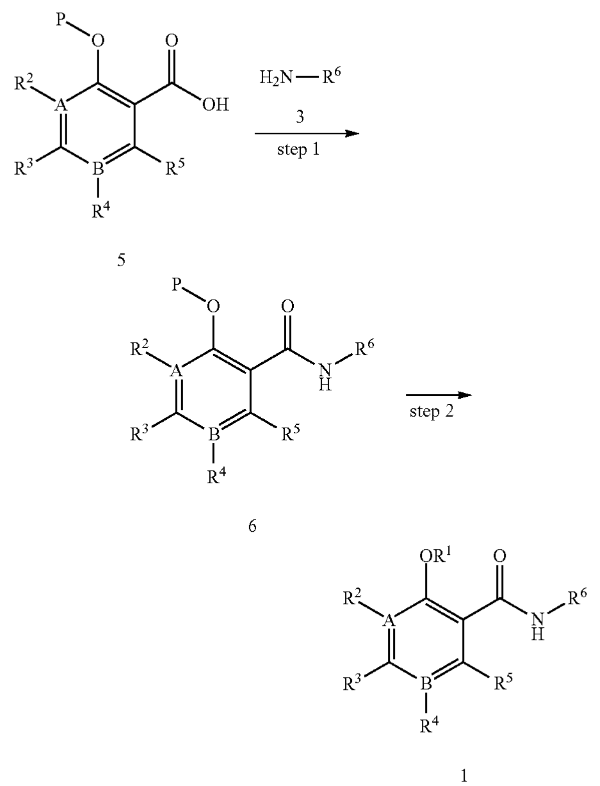
Preparation Method 3

The preparation method of the derivative represented by Formula 1 of the present invention, as shown in the below Reaction Formula 3, is composed of the following steps:

inducing coupling of the compound represented by Formula 2 and the amine compound represented by Formula 3 (step 1); and

inducing deprotection of the protected hydroxy group of the compound represented by Formula 6 prepared in step (step 2).

[Reaction Formula 3]



(In Reaction Formula 3, R^1 is hydrogen, R^2~R^6, A and B are as defined in Formula 1, and P is a protecting group).

In step 1 of the preparation method 3 of the present invention, the compound represented by Formula 6 is prepared as follows: the aryl acid compound having protected hydroxy group represented by Formula 5 is dissolved in an organic solvent in the presence of argon gas; the amine compound represented by Formula 3 is added thereto; and the mixture is reflux-stirred to give the compound represented by Formula 6.

At this time, the conditions for the coupling reaction of step 1 are as described in the preparation method 2.

The protecting group P to protect hydroxy group is methyl group, t-butyl group, benzyl group, acetyl group, phenylcarbonyl group, pivaloyl group, t-butyldimethylsilyl (TBDMS) group, t-butyldiphenylsilyl (TBDPS) group, or methoxymethyl (MOM) group.

In step 2, the hydroxy group of the compound represented by Formula 6 prepared in step 1 is deprotected to give the compound represented by Formula 1b.

The deprotection is performed by the conventional method generally used in this field to deprotect the hydroxy group protected by the protecting group P.

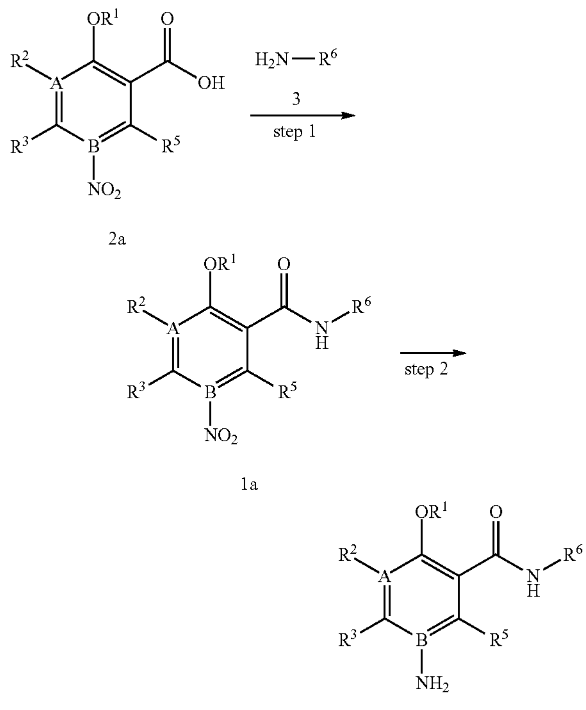
Preparation Method 4

The preparation method of the derivative represented by Formula 1 of the present invention, as shown in the below Reaction Formula 4, is composed of the following steps:

inducing coupling of the 2-hydroxyaryl acid compound represented by Formula 2a and the amine compound represented by Formula 3 (step 1); and

inducing reduction of the compound represented by Formula 1a prepared in step 1 (step 2).

[Reaction Formula 4]



2a 1a 1b

(In Formula 4, R^1~R^3, R^5, R^6, A and B are as defined in Formula 1; 1a and 1b are the compounds of Formula 1; 2a is the compound of Formula 1).

In the preparation method 4 of the present invention, the 2-hydroxyarylamide derivative represented by Formula 1a is prepared as follows: the 2-hydroxyaryl acid compound represented by Formula 2a is dissolved in an organic solvent in the presence of argon gas; a chlorinating agent is added thereto in the presence of a base; the amine compound represented by Formula 3 is added thereto; and the mixture is reflux-stirred to give the 2-hydroxyarylamide derivative represented by Formula 1a.

At this time, the conditions for the coupling reaction of step 1 are as described in the preparation method 2.

In step 2, the compound represented by Formula 1b is prepared by reducing the compound represented by Formula 1a prepared in step 1 using a reducing agent. More precisely, nitro group of the compound represented by Formula 1a is reduced to amine group of the compound represented by Formula 1b in this step.

At this time, the usable reducing agent herein is ammonium chloride (NH_4Cl) or hydrogen (H_2) gas, and preferably ammonium chloride (NH_4Cl).

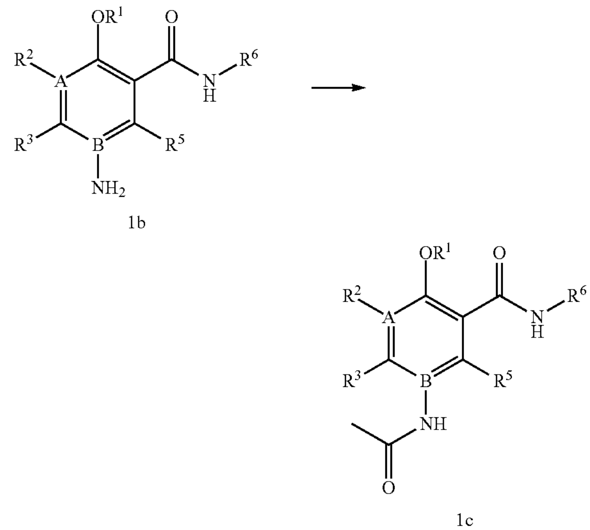
The acceptable catalyst for the above reduction is iron powder, Pd/C, $Pd(OAc)_2$, or PtO_2, and preferably iron powder.

The usable organic solvent herein can be methanol, ethanol, isopropanol, tetrahydrofurane, distilled water, or a mixed solvent thereof, which has no effect on the reaction, and preferably isopropanol.

Preparation Method 5

The preparation method of the derivative of Formula of the present invention, as shown in the below Reaction Formula 5, includes the step of preparing the compound represented by Formula 1c through acylation of the compound represented by Formula 1b:

[Reaction Formula 5]



1b 1c

(In Formula 5, R^1~R^3, R^5, R^6, A and B are as defined in Formula 1; 1b and 1c are the compounds of Formula 1).

In the preparation method 5 of the present invention, the 2-hydroxyarylamide derivative represented by Formula 1c is prepared by reacting amine group of the 2-hydroxyarylamide compound represented by Formula 1b with an acylating agent.

The acylating agent herein is acetic anhydride or acetyl chloride, and preferably acetic anhydride.

The usable organic solvent herein can be acetic acid which does not affect the reaction.

The present invention also provides a pharmaceutical composition for preventing or treating cancer comprising the 2-hydroxyarylamide derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof as an active ingredient.

The cancer herein includes colorectal cancer, lung cancer, breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, and stomach cancer.

The 2-hydroxyarylamide derivative represented by Formula 1 of the present invention was confirmed by the investigation of TMPRSS4 serine protease activity using peptide substrate to inhibit the activity of TMPRSS4 serine protease dose-dependently. In particular, the compounds of Examples 1, 2, 4, 6, 8, 9, 16, 21-23, 26, 32, 33, 36, 39, 65, 66, 70, 71, 73, 75 demonstrated 51~100% inhibitory effect at the concentration of 10 μM (see Experimental Example 1 and Table 2).

The inhibitory effect on the infiltration of colorectal cancer cells expressing TMPRSS4 was investigated. As a result, the compounds of Examples 1, 8, 19, 22, 25, 27, 28, 32, 33, 36, 37, 53, 55 and 65 were confirmed to inhibit the infiltration up to 26~81%. In particular, the compound of Example 19 inhibited 81% of the infiltration (see Experimental Example 2 and Table 3).

Therefore, it was confirmed that the compound of the present invention is excellent in the inhibition of the activity of TMPRSS4 serine protease and the suppression of the infiltration of TMPRSS4-expressed cancer cells, and thus can be useful as a composition for preventing or treating cancer by inhibiting TMPRSS4 over-expressed in cancer cells, particularly, colorectal cancer, lung cancer, breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, or stomach cancer cells.

The present invention also provides a pharmaceutical composition for inhibiting TMPRSS4 (transmembrane protease serine-4) which comprises the 2-hydroxyarylamide derivative represented by the above Formula 1 or the pharmaceutically acceptable salt thereof as an active ingredient.

The present invention also provides a pharmaceutical composition for suppressing cancer metastasis which comprises the 2-hydroxyarylamide derivative represented by the above Formula 1 or the pharmaceutically acceptable salt thereof as an active ingredient.

The 2-hydroxyarylamide derivative represented by Formula 1 of the present invention has excellent effect of inhibiting the activity of TMPRSS4 serine protease which is an important mediator for infiltration, metastasis, migration, and adhesion as well as EMP (epithelial mesenchymal transition) in human epithelial cancer cells. That is, the derivative of the present invention is excellent in inhibiting cancer cell infiltration and metastasis particularly induced by TMPRSS4 serine protease (see Experimental Examples 1 and 2).

The pharmaceutical composition comprising the 2-hydroxyarylamide derivative represented by the above Formula 1 or the pharmaceutically acceptable salt thereof as an active ingredient of the present invention can be administered orally or parenterally and be used in general forms of pharmaceutical formulation, but not always limited thereto.

The formulations for oral administration are exemplified by tablets, pills, hard/soft capsules, solutions, suspensions, emulsions, syrups, granules, and elixirs, etc. These formulations can include diluents (for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, and/or glycine) and lubricants (for example, silica, talc, stearate and its magnesium or calcium salt, and/or polyethylene glycol) in addition to the active ingredient. Tablets can include binding agents such as magnesium aluminum silicate, starch paste, gelatin, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrolidone, and if necessary disintegrating agents such as starch, agarose, alginic acid or its sodium salt or azeotropic mixtures and/or absorbents, coloring agents, flavors, and sweeteners can be additionally included thereto.

The pharmaceutical composition comprising the 2-hydroxyarylamide derivative represented by Formula 1 as an active ingredient of the present invention can be administered by parenterally and the parenteral administration includes subcutaneous injection, intravenous injection, intramuscular injection and intrathoracic injection.

To prepare the pharmaceutical composition of the present invention as a formulation for parenteral administration, the 2-hydroxyarylamide derivative represented by Formula 1 or the pharmaceutically acceptable salt thereof is mixed with a stabilizer or a buffering agent to produce a solution or suspension, which is then formulated as ampoules or vials. The composition can be sterilized and/or can additionally include preservatives, resolvents, stabilizers, wetting agents, emulsifiers, sweetening agents, pigments, flavoring agents, osmosis controlling salts, buffering agents, coating agents, or antioxidants. The composition can also include other therapeutically valuable additives. The composition can be formulated by the conventional method such as mixing, granulation, or coating.

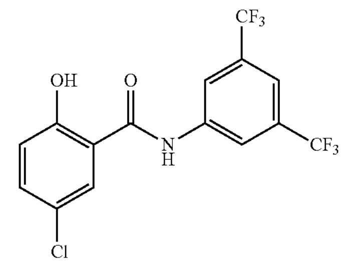
The effective dosage of the pharmaceutical composition comprising the 2-hydroxyarylamide derivative represented by Formula 1 as an active ingredient of the present invention can be determined according to age, weight, gender, administration method, health condition, and severity of disease. The preferable dosage is 0.01~200 mg/kg per day, which can be administered orally or parenterally several times a day or preferably 1~3 times a day according to the decision of a doctor or a pharmacist.

Practical and presently preferred embodiments of the present invention are illustrative as shown in the following Examples, Experimental Examples and Manufacturing Examples.

However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

EXAMPLE 1

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide



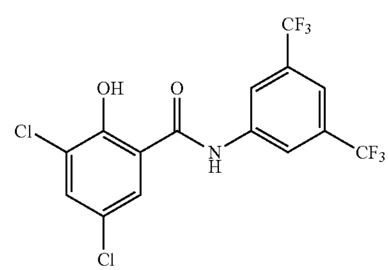
To 30 ml of toluene were added 5-chlorosalicylic acid (862 mg, 5 mmol), 3,5-bis(trifluoromethyl)aniline (1.37 g, 6 mmol), and phosphoroustrichloride (755 mg, 5.5 mmol) in the presence of argon gas, followed by stirring for 6 hours through heat-reflux. Sodium hydrogen carbonate was added to the mixture to adjust pH to 7, followed by concentration under reduced pressure. The mixture was dissolved in 60 ml of ethylacetate, which was washed with water (40 ml×2). The organic layer was concentrated under reduced pressure, followed by column chromatography to give 1.09 g of the target compound (yield: 57%).

m.p: 172-173° C.;

^{1}H-NMR (300 MHz, DMSO-d^6): δ 7.05 (1H, d, J=8.7 Hz), 7.49 (1H, dd, J=8.7, 2.7 Hz), 7.85 (1H, s), 7.87 (1H, d, J=2.7 Hz), 8.45 (2H, s), 10.85 (1H, s), 11.39 (1H, s).

EXAMPLE 2

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)3,5-dichloro-2-hydroxybenzamide



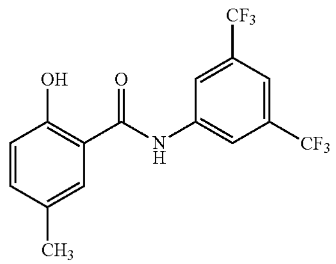
550 mg of the target compound (yield: 26%) was obtained by the same manner as described in Example 1 except that 3,5-dichloro-2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

m.p: 141-143° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.84 (s, 1H), 8.00 (s, 1H), 8.01 (s, 1H), 8.41 (s, 2H), 11.13 (s, 1H).

EXAMPLE 3

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-methylbenzamide



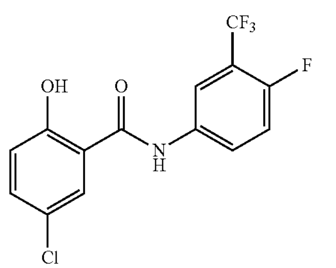
400 mg of the target compound (yield: 22%) was obtained by the same manner as described in Example 1 except that 2-hydroxy-5-methylbenzoic acid was used instead of 5-chlorosalicylic acid.

m.p: 145-147° C.;

^{1}H-NMR (300 MHz, DMSO-D^6) δ 2.28 (s, 3H), 6.90 (d, J=5.0 Hz, 1H), 7.26 (dd, J=2.3, 2.0 Hz, 1H), 7.69 (s, 1H), 7.83 (s, 1H), 8.46 (s, 2H), 10.81 (s, 1H), 10.86 (s, 1H).

EXAMPLE 4

Preparation of 5-chloro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide



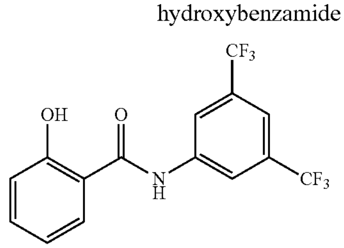
982 mg of the target compound (yield: 59%) was obtained by the same manner as described in Example 1 except that 4-fluoro-3-(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 203-205° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.02 (d, J=8.8 Hz, 1H) 7.56-7.45 (m, 2H), 7.46-7.57 (m, 1H), 8.02-7.98 (m, 1H), 8.19 (dd, J=2.1, 2.0 Hz, 1H), 10.62 (s, 1H), 11.55 (s, 1H).

EXAMPLE 5

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide



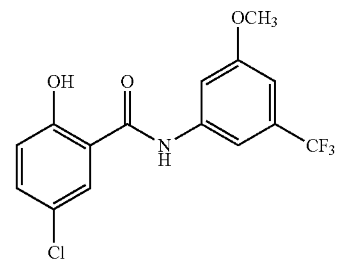
594 mg of the target compound (yield: 34%) was obtained by the same manner as described in Example 1 except that 2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

m.p: 181-182° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.02-6.96 (m, 2H), 7.48-7.42 (m, 1H), 7.87-7.83 (m, 2H), 8.46 (s, 2H), 10.85 (s, 1H).

EXAMPLE 6

Preparation of 5-chloro-2-hydroxy-N-(3-methoxy-5-(trifluoromethyl)phenyl)benzamide



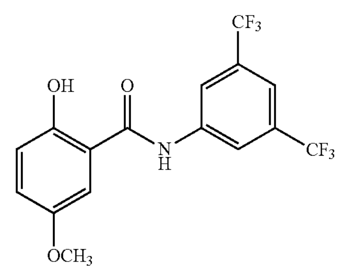
847 mg of the target compound (yield: 49%) was obtained by the same manner as described in Example 1 except that 3-methoxy-5-(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 191-192° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 3.84 (s, 3H) 7.01-7.04 (m, 2H) 7.47 (dd, J=8.8, 2.6 Hz, 1H), 7.60 (s, 1H), 7.76 (s, 1H), 7.88 (d, J=2.6 Hz, 1H), 10.57 (s, 1H), 11.53 (s, 1H).

EXAMPLE 7

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-methoxybenzamide



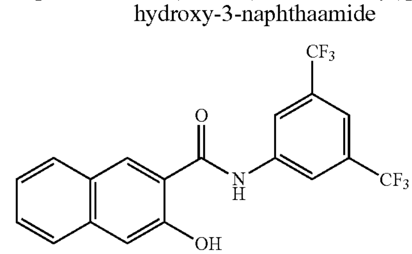
986 mg of the target compound (yield: 52%) was obtained by the same manner as described in Example 1 except that 2-hydroxy-5-methoxybenzoic acid was used instead of 5-chlorosalicylic acid.

m.p: 208-210° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 6.96-6.6.94 (d, J=8.9 Hz, 1H), 3.75 (s, 3H), 7.06-7.10 (dd, J=8.9, 3.1 Hz, 1H), 7.42 (d, J=3.0 Hz, 1H), 7.81 (s, 1H), 8.45 (s, 2H), 10.83 (s, 1H), 10.95 (s, 1H).

EXAMPLE 8

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-3-naphthaamide



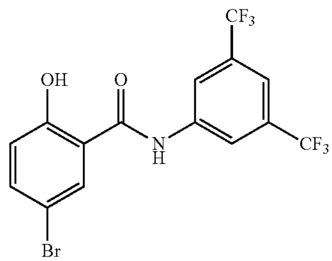
340 mg of the target compound (yield: 17%) was obtained by the same manner as described in Example 1 except that 3-hydroxy-2-naphthoic acid was used instead of 5-chlorosalicylic acid.

m.p: 226-229° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.34-7.38 (m, 2H), 7.49-7.53 (m, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.84 (s, 1H), 7.92 (d, J=7.7 Hz, 1H), 8.40 (s, 1H), 8.50 (s, 2H), 10.99 (s, 1H).

EXAMPLE 9

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-bromo-2-hydroxybenzamide



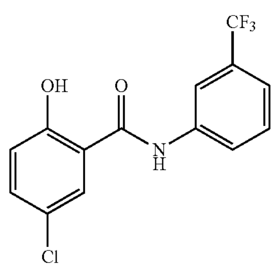
340 mg of the target compound (yield: 17%) was obtained by the same manner as described in Example 1 except that 2-hydroxy-5-bromobenzoic acid was used instead of 5-chlorosalicylic acid.

m.p: 194-195° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 6.98 (d, J=8.3 Hz, 1H), 7.60 (dd, J=8.8, 2.6 Hz, 1H), 7.84 (s, 1H), 7.97 (d, J=2.5 Hz, 1H), 8.44 (s, 2H), 10.85 (s, 1H), 11.41 (s, 1H).

EXAMPLE 10

Preparation of 5-chloro-N-(3-(trifluoromethyl)phenyl)-2-hydroxybenzamide



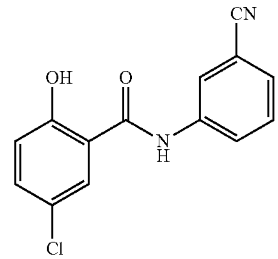
805 mg of the target compound (yield: 51%) was obtained by the same manner as described in Example 1 except that 3-(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 181-182° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.02 (d, J=8.8 Hz, 1H), 7.45-7.50 (m, 2H), 7.61 (dd, J=8.0, 8.0 Hz, 1H), 7.89 (d, J=2.6 Hz, 1H), 7.94 (d, J=8.3 Hz, 1H), 8.20 (s, 1H), 10.63 (s, 1H), 11.57 (s, 1H).

EXAMPLE 11

Preparation of 5-chloro-N-(3-cyanophenyl)-2-hydroxybenzamide



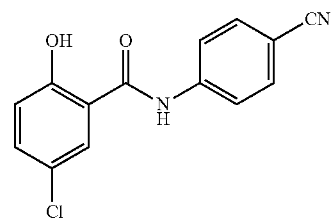
286 mg of the target compound (yield: 21%) was obtained by the same manner as described in Example 1 except that 3-(cyano)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 240-241° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.02 (d, J=8.8 Hz, 1H), 7.45-7.49 (dd, J=8.8, 2.6 Hz, 1H), 7.55-7.61 (m, 2H), 7.86 (d, J=2.6 Hz, 1H), 7.95-7.99 (m, 1H), 8.20 (s, 1H), 10.62 (s, 1H), 11.56 (s, 1H).

EXAMPLE 12

Preparation of 5-chloro-N-(4-cyanophenyl)-2-hydroxybenzamide



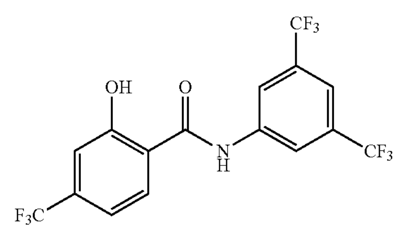
96 mg of the target compound (yield: 7%) was obtained by the same manner as described in Example 1 except that 4-(cyano)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 246-247° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.00 (d, J=8.8 Hz, 1H), 7.43-7.47 (dd, J=8.8, 2.6 Hz, 1H), 7.81-7.84 (m, 3H), 7.91 (d, J=8.7 Hz, 2H), 10.82 (s, 1H).

EXAMPLE 13

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-4-(trifluoromethyl)-2-hydroxybenzamide

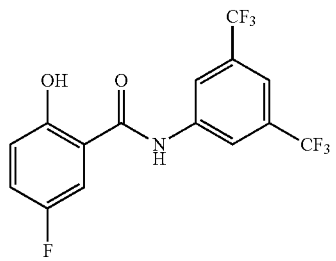


647 mg of the target compound (yield: 31%) was obtained by the same manner as described in Example 1 except that 3-trifluoromethyl-2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.30 (d, J=7.7 Hz, 2H), 7.85 (s, 1H), 7.92 (d, J=8.0 Hz, 1H), 8.44 (s, 2H), 10.94 (s, 1H), 11.48 (s, 1H).

EXAMPLE 14

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-fluoro-2-hydroxybenzamide



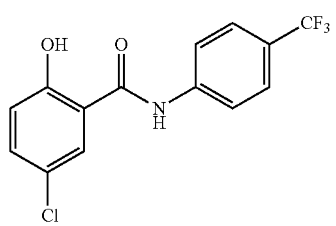
881 mg of the target compound (yield: 48%) was obtained by the same manner as described in Example 1 except that 3-fluoro-2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

m.p: 187-178° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.01-7.05 (dd, J=9.0, 4.6 Hz, 1H), 7.29-7.36 (m, 1H), 7.63-7.67 (dd, J=9.4, 3.2 Hz, 1H), 7.84 (s, 1H), 8.45 (s, 1H), 10.82 (s, 1H), 11.21 (s, 1H).

EXAMPLE 15

Preparation of 5-chloro-N-(4-(trifluoromethyl)phenyl)-2-hydroxybenzamide



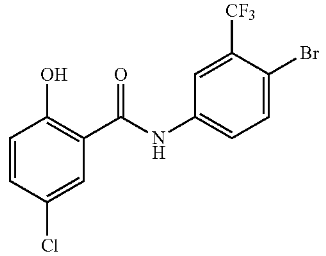
286 mg of the target compound (yield: 21%) was obtained by the same manner as described in Example 1 except that 4-(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 222-223° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.02 (d, J=8.8 Hz, 1H), 7.45-7.49 (dd, J=8.8, 2.7 Hz, 1H), 7.74 (d, J=8.6 Hz, 2H), 7.88 (d, J=2.6 Hz, 1H), 7.94 (d, J=8.5 Hz, 1H), 10.65 (s, 1H), 11.56 (s, 1H).

EXAMPLE 16

Preparation of N-(4-bromo-3-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamine

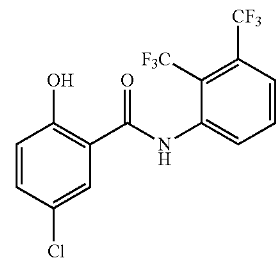


513 mg of the target compound (yield: 26%) was obtained by the same manner as described in Example 1 except that 4-bromo-3-(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.02 (d, J=8.8 Hz, 1H), 7.44-7.48 (dd, J=8.8, 2.6 Hz, 1H), 7.85-7.93 (m, 3H), 8.29 (s, 1H), 10.65 (s, 1H), 11.53 (s, 1H).

EXAMPLE 17

Preparation of 5-chloro-N-(3-(trifluoromethyl)-2-methylphenyl)-2-hydroxybenzamide



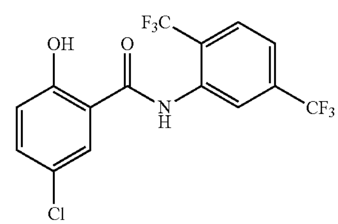
594 mg of the target compound (yield: 36%) was obtained by the same manner as described in Example 1 except that 2,3-bis(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 163-164° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 2.37 (s, 3H), 7.04 (d, J=8.8 Hz, 1H), 7.42-7.51 (m, 2H), 7.59 (d, J=7.6 Hz, 1H), 7.97-8.01 (m, 2H), 10.44 (s, 1H), 12.09 (s, 1H).

EXAMPLE 18

Preparation of N-(2,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamine



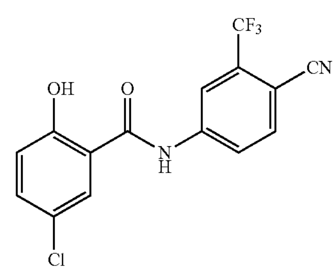
556 mg of the target compound (yield: 29%) was obtained by the same manner as described in Example 1 except that 2,5-bis(trifluoro)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 202-203° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.06 (d, J=8.8 Hz, 1H), 7.51-7.55 (dd, J=8.8, 2.8 Hz, 1H), 7.75 (d, J=8.3 Hz, 1H), 7.97 (d, J=2.8 Hz, 1H), 8.03 (s, 1H), 8.73 (s, 1H), 11.04 (s, 1H), 12.36 (s, 1H).

EXAMPLE 19

Preparation of 5-chloro-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide



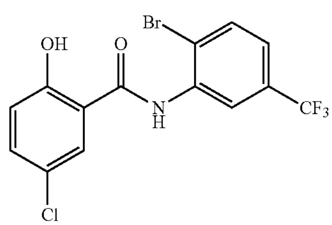
273 mg of the target compound (yield: 16%) was obtained by the same manner as described in Example 1 except that 3-(trifluoromethyl)-4-(cyano)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 214-215° C.;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 7.03 (d, J=8.8 Hz, 1H), 7.46-7.50 (dd, J=8.8, 2.6 Hz, 1H), 7.79 (d, J=2.6 Hz, 1H), 8.15 (s, 2H), 8.42 (s, 1H), 10.97 (s, 1H), 11.34 (s, 1H).

EXAMPLE 20

Preparation of N-(2-bromo-5-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide



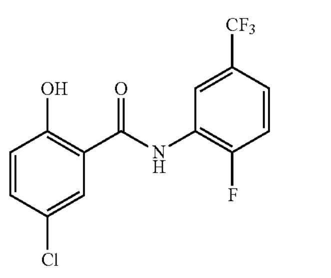
868 mg of the target compound (yield: 44%) was obtained by the same manner as described in Example 1 except that 2-(bromo)-5-(trifluoro)aniline was used instead of 3,5-bis (trifluoromethyl)aniline.

m.p: 174-175° C.;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 7.09 (d, J=8.8 Hz, 1H), 7.44-7.53 (m, 2H), 7.95-7.97 (m, 2H), 8.80 (s, 1H), 11.02 (s, 1H), 12.37 (s, 1H).

EXAMPLE 21

Preparation of 5-chloro-N-(2-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxybenzamide



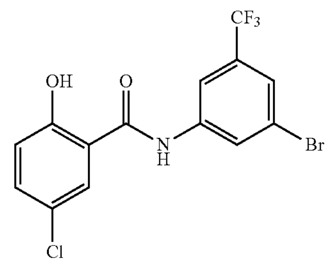
634 mg of the target compound (yield: 38%) was obtained by the same manner as described in Example 1 except that 3-(trifluoromethyl)-6-(fluoro)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 199-200° C.;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 7.06 (d, J=8.8 Hz, 1H), 7.49-7.53 (m, 1H), 7.59 (d, J=8.1 Hz, 2H), 7.94 (d, J=2.8 Hz, 1H), 8.72 (s, 1H), 10.91 (s, 1H), 12.25 (s, 1H).

EXAMPLE 22

Preparation of N-(3-bromo-5-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide



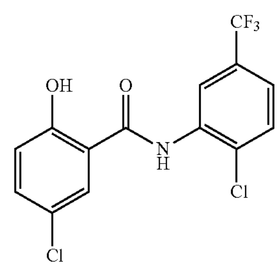
1010 mg of the target compound (yield: 51%) was obtained by the same manner as described in Example 1 except that 3-(trifluoromethyl)-5-(bromo)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 200-202° C.;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 7.03 (d, J=8.8 Hz, 1H), 7.46-7.49 (dd, J=8.8, 2.6 Hz, 1H), 7.71 (s, 1H), 7.84 (d, J=2.6 Hz, 1H), 8.15 (s, 1H), 8.27 (s, 1H), 10.72 (s, 1H), 11.45 (s, 1H).

EXAMPLE 23

Preparation of 5-chloro-N-(2-chloro-5-(trifluoromethyl)phenyl)-2-hydroxybenzamide



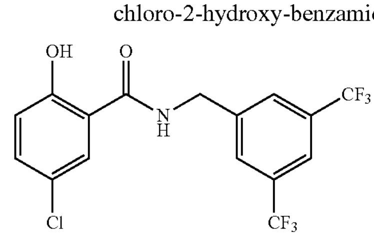
1400 mg of the target compound (yield: 80%) was obtained by the same manner as described in Example 1 except that 3-(trifluoromethyl)-6-(chloro)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 180-182° C.;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 7.08 (d, J=8.8 Hz, 1H), 7.50-7.56 (m, 2H), 7.82 (d, J=8.4 Hz, 1H), 7.97 (d, J=2.8 Hz, 1H), 8.87 (d, J=2.0 Hz, 1H), 11.19 (s, 1H), 12.43 (s, 1H).

EXAMPLE 24

Preparation of N-(3,5-bis-trifluoromethyl-benzyl)-5-chloro-2-hydroxy-benzamide



To 12 ml of dichloromethane were added 5-chlorosalicylic acid (690 mg, 4 mmol), 3,5-bis(trifluoromethyl)aniline (972 mg, 4 mmol), EDCI (1.2 g, 8 mmol), and DMAP (49 mg, 0.4

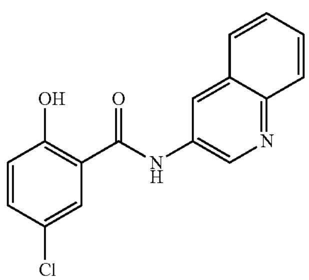
mmol) in the presence of argon gas, followed by stirring for 12 hours at room temperature. The mixture was concentrated under reduced pressure, and then dissolved in 60 ml of ethylacetate, which was washed with water (40 ml×2). The organic layer was concentrated under reduced pressure, followed by column chromatography (developing solvent: hexane/ethylacetate=1/10) to give 609 mg of the target compound (yield: 38%).

m.p: 125-127° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 4.68 (d, J=5.8 Hz, 2H), 6.97 (d, J=8.8 Hz, 1H), 7.44 (dd, J=8.8, 2.6 Hz, 1H), 7.89 (d, J=2.7 Hz, 1H), 8.03 (d, J=10.9 Hz, 3H), 9.41 (t, J=5.8 Hz, 1H), 12.09 (s, 1H).

EXAMPLE 25

Preparation of 5-chloro-2-hydroxy-N-quinoline-3-yl-benzamide



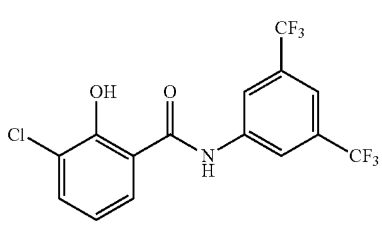
104 mg of the target compound (yield: 7%) was obtained by the same manner as described in Example 1 except that quinoline-3-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 253-255° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.05-7.12 (m, 1H), 7.46-7.67 (m, 3H), 7.98 (dd J=6.6 Hz, 3H), 8.79 (s, 1H), 9.04 (s, 1H), 10.77 (s, 1H), 11.73 (s, br, 1H).

EXAMPLE 26

Preparation of N-(3,5-bis-trifluoromethyl-phenyl)-3-chloro-2-hydroxy-benzamide



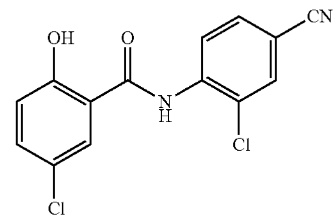
1.13 mg of the target compound (yield: 59%) was obtained by the same manner as described in Example 1 except that 3-chloro-2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

m.p: 156-157° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.00-7.07 (m, 1H), 7.66-7.71 (m, 1H), 7.88-7.94 (m, 2H), 8.44 (d, J=3.4 Hz, 2H), 11.02 (s, 1H), 11.94 (s, br, 1H).

EXAMPLE 27

Preparation of 5-chloro-N-(2-chloro-4-cyano-phenyl)-2-hydroxy-benzamide

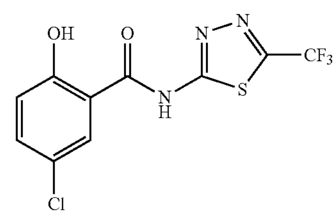


415 mg of the target compound (yield: 27%) was obtained by the same manner as described in Example 1 except that 4-(cyano)-3-(chloro)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.08 (d, J=8.8 Hz, 1H), 7.52 (dd, J=8.8, 2.8 Hz, 1H), 7.87 (dd, J=8.7, 2.0 Hz, 1H), 7.95 (d, J=2.8 Hz, 1H), 8.17 (d, J=1.8 Hz, 1H), 8.70 (d, J=8.7 Hz, 1H), 11.24 (s, 1H), 12.42 (s, br, 1H).

EXAMPLE 28

Preparation of 5-chloro-2-hydroxy-N-(5-trifluoromethyl-[1,3,4]thiadiazole-2-yl)-benzamide

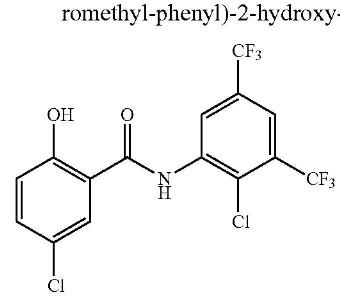


728 mg of the target compound (yield: 45%) was obtained by the same manner as described in Example 1 except that 5-(trifluoromethyl)-1,3,4-thiadiazole-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 6.96 (d, J=8.8 Hz, 1H), 7.42 (dd, J=8.8, 2.8 Hz, 1H), 7.83 (d, J=2.8 Hz, 1H).

EXAMPLE 29

Preparation of 5-chloro-N-(2-chloro-3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-benzamide

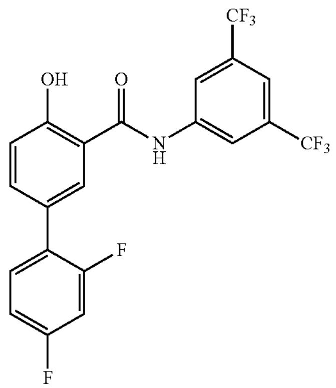


878 mg of the target compound (yield: 42%) was obtained by the same manner as described in Example 1 except that 3,5-bis(trifluoromethyl)-6-(chloro)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ7.09 (d, J=8.7 Hz, 1H), 7.53 (dd, J=8.8, 2.8 Hz, 1H), 7.93 (s, 1H), 7.95 (d, J=2.8 Hz, 1H), 9.14 (s, 1H), 11.31 (s, 1H), 12.45 (s, 1H).

EXAMPLE 30

Preparation of N-(2-chloro-3,5-bis(trifluoromethyl)phenyl)-4',6'-difluoro-4-hydroxybiphenyl-3-carboxamide

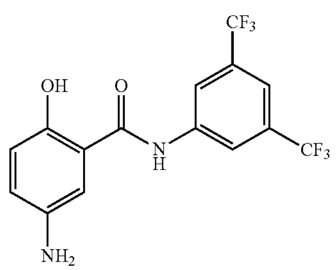


1360 mg of the target compound (yield: 59%) was obtained by the same manner as described in Example 1 except that 4',6'-difluoro-4-hydroxybiphenyl-3-carboxylic acid was used instead of 5-chlorosalicylic acid.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.13 (d, J=8.6 Hz, 1H), 7.20-7.25 (m, 1H), 7.35-7.42 (m, 1H), 7.57-7.65 (m, 2H), 7.85 (s, 1H), 8.02 (s, 1H), 8.48 (s, 2H), 10.90 (s, 1H), 11.47 (s, 1H).

EXAMPLE 31

Preparation of 5-amino-N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide



Step 1: Preparation of N-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-5-nitro-benzamide

517 mg of the target compound (yield: 26%) was obtained by the same manner as described in Example 1 except that 2-hydroxy-5-nitrobenzoic acid was used instead of 5-chlorosalicylic acid.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.17 (d, J=8.9 Hz, 1H), 7.87 (s, 1H), 8.30 (d, J=9.1 Hz, 1H), 8.45 (s, 2H), 8.69 (s, 1H), 11.13 (s, 1H).

Step 2: Preparation of 5-amino-N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide

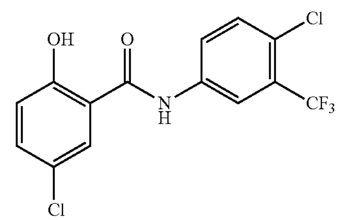
N-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-5-nitrobenzamide (400 mg, 1.4 mmol) prepared in step 1 was dissolved in 4.2 . of isopropanol (IPA), to which 3 g of iron powder and 3 . of NH_4Cl saturated solution were added.

The mixture was stirred for 3 hours. The reaction mixture was filtered by using silica gel and celite. The filtered solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethylacetate=5:1) to give 280 mg of the target compound (yield: 77%).

^{1}H-NMR (300 MHz, DMSO-d^6) δ 4.79 (s, 2H), 6.76 (d, J=8.0 Hz, 2H), 7.08 (s, 1H), 7.79 (s, 1H), 8.44 (s, 2H), 10.37 (s, 1H), 10.82 (s, 1H).

EXAMPLE 32

Preparation of 5-chloro-N-(4-chloro-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide



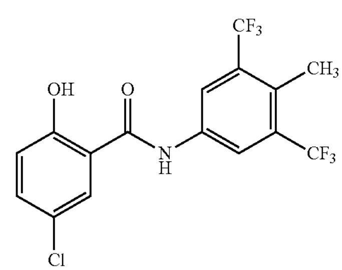
655 mg of the target compound (yield: 38%) was obtained by the same manner as described in Example 1 except that 3-(chloro)-4-(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 230-232° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.02 (d, J=8.7 Hz, 1H), 7.46 (d, J=7.5 Hz, 1H), 7.72 (d, J=9.0 Hz, 1H), 7.85 (s, 1H), 7.99 (d, J=8.4 Hz, 1H), 8.30 (s, 1H), 10.68 (s, 1H).

EXAMPLE 33

Preparation of 5-chloro-2-hydroxy-N-(4-methyl-3,5-bis(trifluoromethyl)phenyl)benzamide



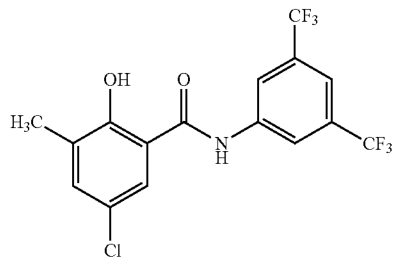
1010 mg of the target compound (yield: 51%) was obtained by the same manner as described in Example 1 except that 4-methyl-3,5-bis(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 192-193° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 2.49 (s, 3H), 7.02 (d, J=8.8 Hz, 1H), 7.47 (dd, J=8.8, 2.7 Hz, 1H), 7.87 (d, J=2.6, 1H), 8.41 (s, 2H), 10.75 (s, 1H), 11.48 (s, 1H).

EXAMPLE 34

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxy-3-methylbenzamide



Step 1: Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-methoxy-3-methylbenzamide

1500 mg of the target compound (yield: 94%) was obtained by the same manner as described in Example 1 except that 5-chloro-2-methoxy-3-methylbenzoic acid was used instead of 5-chlorosalicylic acid.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 2.29 (s, 3H), 3.75 (s, 3H), 7.49-7.51 (m, 2H), 7.83 (s, 1H), 8.41 (s, 2H), 11.00 (s, 1H).

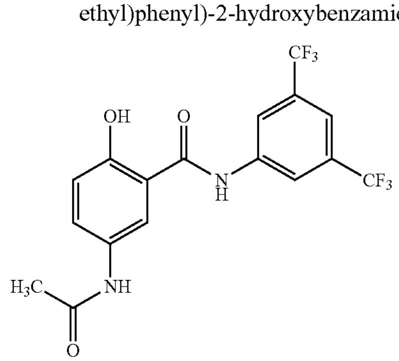
Step 2: Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxy-3-methylbenzamide

N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-methoxy-3-methylbenzamide (1 g, 2.43 mmol) prepared in step 1 was dissolved in CH_2Cl_2 (15 ml), to which boron tribromide (3.54 ml, 12.15 mmol) was added at −70° C., followed by stirring at room temperature for 3 hours. The mixture was dropped in 20 ml of cold ice water, followed by stirring for 30 more minutes. The mixture was cooled down at room temperature, to which aqueous sodium hydroxide was dropped 6~7 drops. Extraction was performed with dichloromethane. The organic extract was mixed, dried over $MgSO_4$, and concentrated under reduced pressure, followed by chromatography (ethylacetate:hexane=1:5) to give 930 mg of the target compound (yield: 96%).

^{1}H-NMR (300 MHz, DMSO-d^6) δ 2.20 (s, 3H), 7.49 (d, J=1.8 Hz, 1H), 7.89 (s, 1H), 7.98 (d, J=2.4 Hz, 1H), 8.43 (s, 2H), 10.91 (s, 1H), 11.86 (s, 1H).

EXAMPLE 35

Preparation of 5-acetamido-N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide

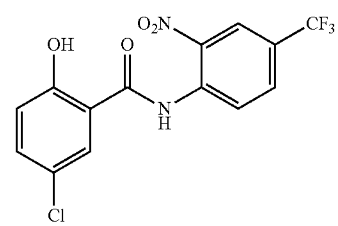


5-Amino-N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide (364.24 mg, 1 mmol) obtained in Example 31 was dissolved in acetic anhydride (0.09 ., 1 mmol), to which AcOH (3 ml) was added, followed by stirring at room temperature for 3 hours. The mixture was extracted by using ethylacetate. The extract was washed with saturated sodium hydrogen carbonate, and dried over $MgSO_4$. After eliminating ethylacetate, the non-purified compound was purified by silica gel column chromatography (ethylacetate:hexane=1:1) to give 340 mg of the target compound (yield: 84%).

^{1}H-NMR (300 MHz, DMSO-d^6) δ 2.01 (s, 3H), 6.94 (d, J=8.8 Hz, 1H), 7.58 (dd, J=8.8, 2.6 Hz, 1H), 7.80 (s, 1H), 7.98 (d, J=2.6 Hz, 1H), 8.44 (s, 2H), 9.87 (s, 1H), 11.18 (s, 2H).

EXAMPLE 36

Preparation of 5-chloro-2-hydroxy-N-(2-nitro-4-trifluoromethyl-phenyl)-benzamide

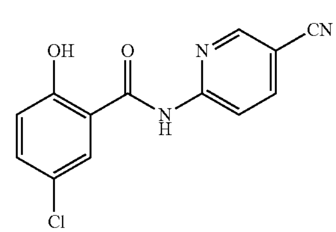


166 mg of the target compound (yield: 9.2%) was obtained by the same manner as described in Example 1 except that 2-nitro-4-(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.08 (dd, J=8.7, 1.2 Hz, 1H), 7.51-7.55 (m, 1H), 7.94 (dd, J=2.7, 1.4 Hz, 1H), 8.15-8.18 (m, 1H), 8.45 (s, 1H), 8.88 (d, J=9.0 Hz, 1H), 12.20 (s, 1H).

EXAMPLE 37

Preparation of 5-chloro-N-(5-cyano-pyridine-2-yl)-2-hydroxy-benzamide



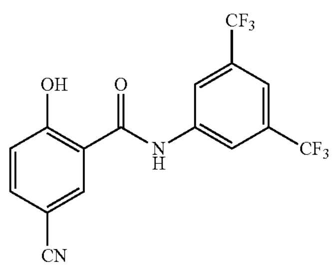
mg of the target compound (yield: 3%) was obtained by the same manner as described in Example 1 except that 6-aminonicotinonitrile was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.09 (d, J=8.8 Hz, 1H), 7.52 (dd, J=8.8, 2.8 Hz, 1H), 7.92 (d, J=2.8 Hz, 1H), 8.32-8.41 (m, 2H), 8.83 (t, J=1.3 Hz, 1H), 11.21 (s, 1H), 12.09 (s, 1H).

EXAMPLE 38

Preparation of N^3-(3,5-bis-trifluoromethyl-phenyl)-4-hydroxy-isophthalamide

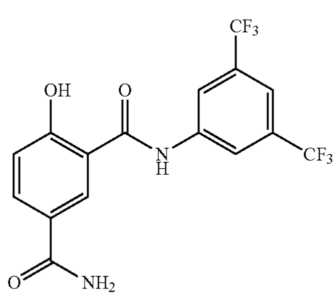
Step 1: Preparation of N-(3,5-bis-trifluoromethyl-phenyl)-5-cyano-2-hydroxy-benzamide



973 mg of the target compound (yield: 52%) was obtained by the same manner as described in Example 1 except that 5-cyano-2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.15 (d, J=8.6 Hz, 1H), 7.85-7.89 (m, 2H), 8.22 (d, J=2.1 Hz, 1H), 8.44 (s, 2H), 10.98 (s, 1H), 12.10 (s, 1H).

Step 2: Preparation of N-(3,5-bis-trifluoromethyl-phenyl)-4-hydroxy-isophthalamide



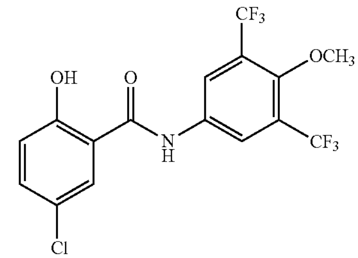
N-(3,5-bis-trifluoromethyl-phenyl)-5-cyano-2-hydroxy-benzamide (150 mg, 0.4 mmol) obtained in step 1 was dissolved in ethanol (1.74 ml) and DMSO (0.8 ml). 1 M NaOH (0.33 ml) was added thereto, to which 30% H_2O_2 (0.33 ml) was added. The reaction mixture was stirred overnight at room temperature. The solution was eliminated under reduced pressure. The residue proceeded to column chromatography (5% MeOH—$CHCl_3$) to give 149 mg of the target compound (yield: 95%).

m.p: 227-228° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.05 (d, J=8.6 Hz, 1H), 7.30-7.32 (m, 1H), 7.86 (s, 1H), 7.92-7.94 (m, 1H), 7.97 (dd, J=8.7, 2.1 Hz, 1H), 8.42 (d, J=2.1 Hz, 1H), 8.49 (s, 2H), 10.98 (s, 1H), 11.65 (s, 1H).

EXAMPLE 39

Preparation of 5-chloro-2-hydroxy-N-(4-methoxy-3,5-bis-trifluoromethyl-phenyl)-benzamide



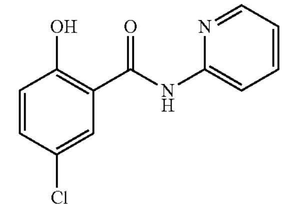
889 mg of the target compound (yield: 43%) was obtained by the same manner as described in Example 1 except that 3-methoxy-2,4-bis(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 168-170° C.;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.02 (d, J=8.82 Hz, 1H), 7.42-7.51 (m, 2H), 7.97 (d, J=0.54 Hz, 1H), 8.08 (s, 2H), 11.39 (s, 1H).

EXAMPLE 40

Preparation of 5-chloro-2-hydroxy-N-(pyridine-2-yl)benzamide

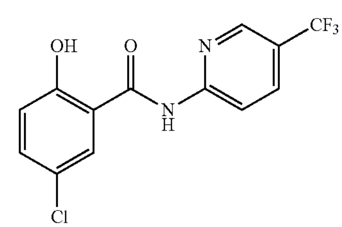


137 mg of the target compound (yield: 11%) was obtained by the same manner as described in Example 1 except that pyridine-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.06 (d, J=8.7 Hz, 1H), 7.17 (dd, J=6.8, 5.1 Hz, 1H), 7.49 (dd, J=8.7, 2.8 Hz, 1H), 7.83-7.88 (m, 1H), 7.96 (d, J=2.7 Hz, 1H), 8.24 (d, J=8.3 Hz, 1H), 8.35 (d, J=3.9 Hz, 1H), 10.95 (bs, 1H).

EXAMPLE 41

Preparation of 5-chloro-2-hydroxy-N-(5-(trifluoromethyl)pyridine-2-yl)benzamide



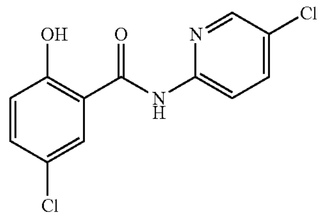
341 mg of the target compound (yield: 26%) was obtained by the same manner as described in Example 1 except that 5-(trifluoromethyl)pyridine-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 241-243° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.08 (d, J=8.7 Hz, 1H), 7.51 (dd, J=8.7, 2.8 Hz, 1H), 7.93 (d, J=2.7 Hz, 1H), 8.26 (dd, J=8.8, 2.2 Hz, 1H), 8.43 (d, J=8.7 Hz, 1H), 8.74 (d, J=1.4 Hz, 1H), 11.18 (bs, 1H).

EXAMPLE 42

Preparation of 5-chloro-N-(5-chloropyridine-2-yl)-2-hydroxybenzamide

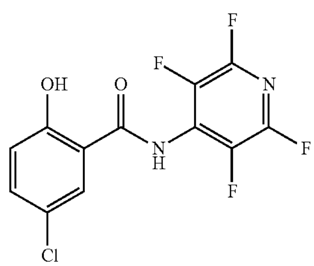


184 mg of the target compound (yield: 13%) was obtained by the same manner as described in Example 1 except that 5-(chloro)pyridine-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.07 (d, J=8.7 Hz, 1H), 7.49 (dd, J=8.7, 2.8 Hz, 1H), 7.94 (d, J=2.7 Hz, 1H), 7.98 (dd, J=8.9, 2.6 Hz, 1H), 8.27 (d, J=8.9 Hz, 1H), 8.41 (d, J=2.1 Hz, 1H), 10.99 (bs, 1H).

EXAMPLE 43

Preparation of 5-chloro-2-hydroxy-N-(perfluoropyridine-4-yl)benzamide

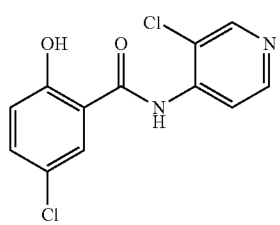


112 mg of the target compound (yield: 7%) was obtained by the same manner as described in Example 1 except that 3-(cyano)benzamine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.07 (d, J=8.8 Hz, 1H), 7.53 (dd, J=8.8, 2.7 Hz, 1H), 7.86 (d, J=2.7 Hz, 1H).

EXAMPLE 44

Preparation of 5-chloro-N-(2-chloropyridine-3-yl)-2-hydroxybenzamide

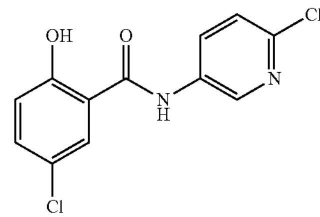


297 mg of the target compound (yield: 21%) was obtained by the same manner as described in Example 1 except that 3-chloropyridine-4-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.08 (d, J=8.8 Hz, 1H), 7.48-7.54 (m, 2H), 7.96 (d, J=2.6 Hz, 2H), 8.19 (d, J=4.5 Hz, 1H), 8.79 (d, J=8.1 Hz, 1H), 11.02 (bs, 1H).

EXAMPLE 45

Preparation of 5-chloro-N-(6-chloropyridine-3-yl)-2-hydroxybenzamide



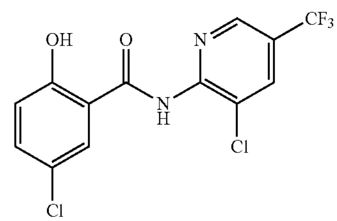
156 mg of the target compound (yield: 11%) was obtained by the same manner as described in Example 1 except that 6-chloropyridine-3-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 250-252° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.01 (d, J=8.7 Hz, 1H), 7.46 (dd, J=8.7, 2.7 Hz, 1H), 7.53 (d, J=8.7 Hz, 1H), 8.20 (dd, J=8.6, 2.7 Hz, 1H), 8.72 (d, J=2.6 Hz, 1H), 10.79 (bs, 1H).

EXAMPLE 46

Preparation of 5-chloro-N-(3-chloro-5-(trifluoromethyl)pyridine-2-yl)-2-hydroxybenzamide



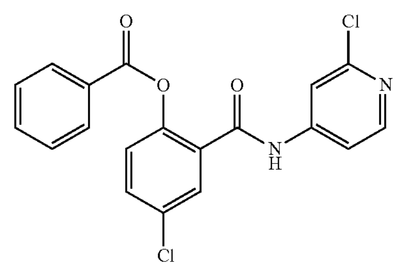
119 mg of the target compound (yield: 8%) was obtained by the same manner as described in Example 1 except that 3-chloro-5-(trifluoromethyl)pyridine-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.21 (d, J=8.7 Hz, 1H), 7.67 (dd, J=8.6, 2.5 Hz, 1H), 7.84 (d, J=2.5 Hz, 1H), 8.61 (s, 1H), 8.91 (s, 1H).

EXAMPLE 47

Preparation of 5-chloro-N-(2-chloropyridine-4-yl)-2-hydroxybenzamide

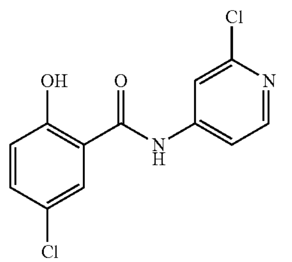
Step 1: Preparation of 4-chloro-2-(2-chloropyridine-4-ylcarbamoyl)phenylbenzonate



4-Chloro-2-(chlorocarbonyl)phenylbenzonate (1.18 mg, 4 mmol) was dissolved in toluene (18 ml). Triethylamine (0.66 mL, 4.8 mmol) was added thereto, to which 4-amino-2-chloropyridine (460 mg, 3.6 mmol) was added, followed by reflux-stirring. Upon completion of the reaction, column chromatography (ethylacetate:hexane=1:5) was performed to give 540 mg of the target compound (yield: 23%).

[1]H-NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, J=5.6, 1.8 Hz, 1H), 7.26 (d, J=8.6 Hz, 1H), 7.48 (d, J=1.6 Hz, 1H), 7.54-7.59 (m, 3H), 7.72 (t, J=7.4 Hz, 1H), 7.92 (d, J=2.5 Hz, 1H), 8.16 (s, 1H), 8.19 (d, J=2.5 Hz, 1H), 8.59 (bs, 1H).

Step 2: Preparation of 5-chloro-N-(2-chloropyridine-4-yl)-2-hydroxybenzamide



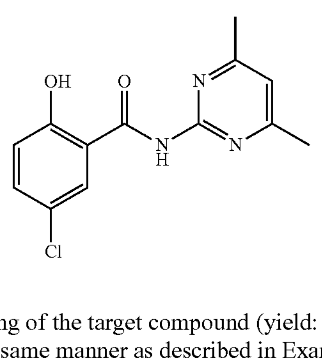
4-Chloro-2-(2-chloropyridine-4-ylcarbamoyl)phenylbenzonate (560 mg, 1.2 mmol) obtained in step 1 was added in the mixed solution of methanol (5 .) and 1,4-dioxane (5 mL), to which potassium carbonate (K_2CO_3, 244 mg, 1.8 mmol) was added. Upon completion of the reaction, column chromatography (ethylacetate:hexane=1:5) was performed to give 272 mg of the target compound (yield: 80%).

m.p: 223-225° C.;

[1]H-NMR (300 MHz, DMSO-d^6) δ 7.03 (d, J=8.8 Hz, 1H), 7.47 (dd, J=8.7, 2.6 Hz, 1H), 7.66 (dd, J=5.6, 1.7 Hz, 1H), 7.77 (d, J=2.6 Hz, 1H), 7.90 (d, J=1.5 Hz, 1H), 8.31 (d, J=5.6 Hz, 1H), 10.78 (s, 1H), 11.36 (s, 1H).

EXAMPLE 48

Preparation of 5-chloro-N-(4,6-dimethylpyrimidine-2-yl)-2-hydroxybenzamide

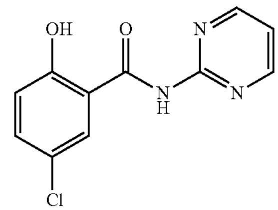


mg of the target compound (yield: 14%) was obtained by the same manner as described in Example 1 except that 4,6-dimethylpyridine-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

[1]H-NMR (300 MHz, DMSO-d^6) δ 2.38 (s, 6H), 7.02 (t, J=4.3 Hz, 1H), 7.47 (dd, J=8.7, 2.6 Hz, 1H), 7.92 (d, J=2.6 Hz, 1H), 10.92 (s, 1H), 11.92 (s, 1H).

EXAMPLE 49

Preparation of 5-chloro-2-hydroxy-N-(pyrimidine-2-yl)benzamide



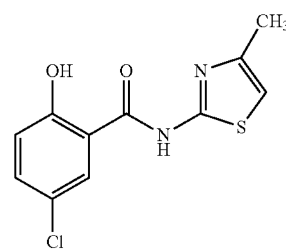
87 mg of the target compound (yield: 29%) was obtained by the same manner as described in Example 1 except that pyridine-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

m.p: 248-251° C.;

[1]H-NMR (300 MHz, DMSO-d^6) δ 7.03 (d, J=8.7 Hz, 1H), 7.26 (t, J=4.8 Hz, 1H), 7.41-7.51 (m, 2H), 7.90 (d, J=2.6 Hz, 1H), 8.71 (d, J=4.8 Hz, 2H), 11.15 (s, 1H).

EXAMPLE 50

Preparation of 5-chloro-2-hydroxy-N-(4-methylthiazole-2-yl)benzamide

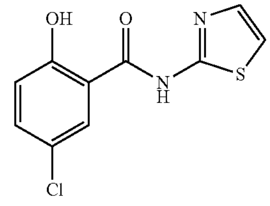


121 mg of the target compound (yield: 9%) was obtained by the same manner as described in Example 1 except that 4-methylthiazole-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

[1]H-NMR (300 MHz, DMSO-d^6) δ 2.27 (s, 3H), 6.79 (s, 1H), 6.96 (d, J=8.7 Hz, 1H), 7.43 (dd, J=8.8, 2.6 Hz, 1H), 7.89 (d, J=2.7 Hz, 1H).

EXAMPLE 51

Preparation of 5-chloro-2-hydroxy-N-(thiazole-2-yl)benzamide

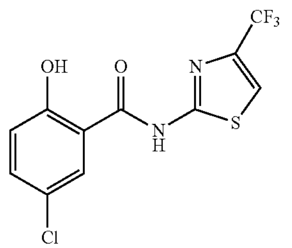


140 mg of the target compound (yield: 11%) was obtained by the same manner as described in Example 1 except that thiazole-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

[1]H-NMR (300 MHz, DMSO-d^6) δ 6.99 (d, J=8.7 Hz, 1H), 7.26 (d, J=3.8 Hz, 1H), 7.46 (dd, J=8.7, 2.5 Hz, 1H), 7.57 (d, J=3.9 Hz, 1H), 7.91 (d, J=2.6 Hz, 1H).

EXAMPLE 52

Preparation of 5-chloro-2-hydroxy-N-(4-(trifluoromethyl)thiazole-2-yl)benzamide

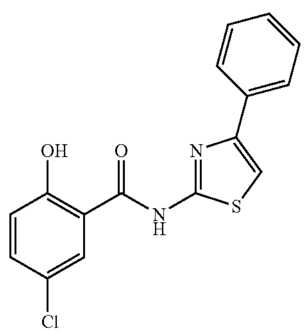


436 mg of the target compound (yield: 27%) was obtained by the same manner as described in Example 1 except that 4-(trifluoromethyl)-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.07 (d, J=8.8 Hz, 1H), 7.52 (dd, J=8.8, 2.6 Hz, 1H), 7.89 (d, J=2.6 Hz, 1H), 8.05 (s, 1H), 11.69 (s, 1H), 12.33 (s, 1H).

EXAMPLE 53

Preparation of 5-chloro-2-hydroxy-N-(4-phenylthiazole-2-yl)benzamide

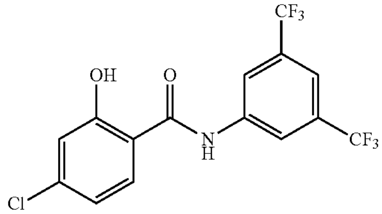


103 mg of the target compound (yield: 26%) was obtained by the same manner as described in Example 1 except that 4-phenylthiazole-2-amine was used instead of 3,5-bis(trifluoromethyl)aniline.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 7.04 (d, J=8.8 Hz, 1H), 7.31 (t, J=7.1 Hz, 1H), 7.41 (t, J=7.4 Hz, 2H), 7.48 (dd, J=8.7, 2.4 Hz, 1H), 7.68 (s, 1H), 7.89 (d, J=7.5 Hz, 1H), 7.93 (d, J=2.7 Hz, 1H), 12.12 (s, 1H).

EXAMPLE 54

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-4-chloro-2-hydroxybenzamide



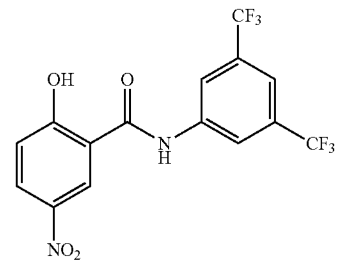
The target compound (yield: 52%) was obtained by the same manner as described in Example 1 except that 4-chloro-2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

mp. 204-205° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 11.52 (brs, 1H), 10.80 (s, 1H), 8.43 (s, 2H), 7.81-7.86 (m, 2H), 7.03-7.06 (m, 2H).

EXAMPLE 55

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-nitrobenzamide



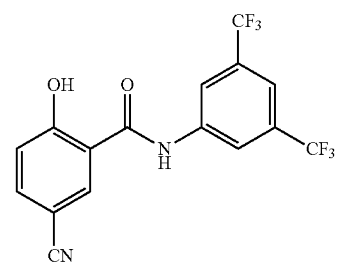
The target compound (yield: 26%) was obtained by the same manner as described in Example 1 except that 2-hydroxy-5-nitrobenzoic acid was used instead of 5-chlorosalicylic acid.

mp. 225-226° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 11.13 (s, 1H), 8.69 (s, 1H), 8.45 (s, 2H), 8.30 (d, J=9.1 Hz, 1H), 7.87 (s, 1H), 7.17 (d, J=8.9 Hz, 1H).

EXAMPLE 56

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-cyano-2-hydroxybenzamide



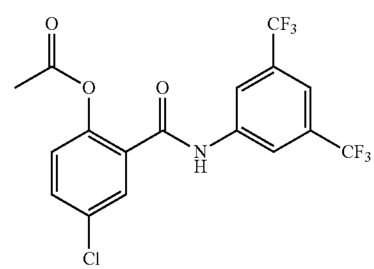
The target compound (yield: 52%) was obtained by the same manner as described in Example 1 except that 5-cyano-2-hydroxybenzoic acid was used instead of 5-chlorosalicylic acid.

mp. 251-253° C.;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 12.10 (brs, 1H), 10.98 (s, 1H), 8.44 (s, 2H), 8.22 (d, J=2.1 Hz, 1H), 7.85-7.89 (m, 2H), 7.15 (d, J=8.6 Hz, 1H).

EXAMPLE 57

Preparation of 2-(3,5-bis(trifluoromethyl)phenylcarbamoyl)-4-chlorophenylacetate



Step 1: Preparation of N-(3,5-bis(trifluoromethyl) phenyl)-5-chloro-2-hydroxybenzamide

The target compound was obtained by the same manner as described in Example 1.

*[1]H-NMR (300 MHz, DMSO-d[6]): δ 7.05 (1H, d, J=8.7 Hz), 7.49 (1H, dd, J=8.7, 2.7 Hz), 7.85 (1H, s), 7.87 (1H, d, J=2.7 Hz), 8.45 (2H, s), 10.85 (1H, s), 11.39 (1H, s).

Step 2: Preparation of 2-(3,5-bis(trifluoromethyl) phenylcarbamoyl)-4-chlorophenylacetate

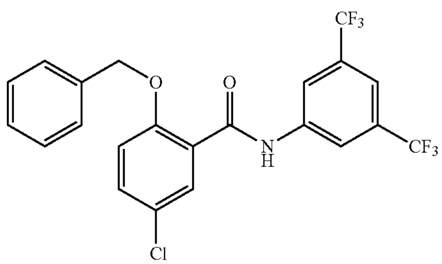
N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide (191.8 mg) obtained in step 1 was dissolved in dimethylformamide (DMF, 1.5 ml), to which acetic anhydride (0.99 ., 10.5 mmol) was added. The reaction mixture was stirred at 100° C. for 4 hours, which was filtered and washed with n-hexane. The washed reactant was dried to give 115.6 mg of the target compound (yield: 54%).

mp. 117-118° C.;

[1]H-NMR (300 MHz, DMSO-d[6]) δ 11.06 (s, 1H), 8.37 (s, 2H), 7.86-7.90 (m, 2H), 7.71 (dd, J=8.7 Hz, J=2.6 Hz, 1H), 7.36 (d, J=8.7 Hz, 1H), 2.23 (s, 3H).

EXAMPLE 58

Preparation of 2-benzyloxy-N-(3,5-bis-trifluoromethyl-phenyl)-5-chlorobenzamide



Step 1: Preparation of N-(3,5-bis(trifluoromethyl) phenyl)-5-chloro-2-hydroxybenzamide

The target compound was obtained by the same manner as described in Example 1.

[1]H-NMR (300 MHz, DMSO-d[6]): δ 7.05 (1H, d, J=8.7 Hz), 7.49 (1H, dd, J=8.7, 2.7 Hz), 7.85 (1H, s), 7.87 (1H, d, J=2.7 Hz), 8.45 (2H, s), 10.85 (1H, s), 11.39 (1H, s).

Step 2: Preparation of 2-benzyloxy-N-(3,5-bis-trifluoromethyl-phenyl)-5-chlorobenzamide

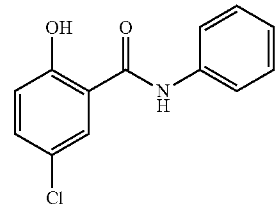
N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide (191.8 mg) obtained in step 1 was dissolved in dimethylformamide (DMF, 1.5 ml), to which benzylbromide (0.07 ., 0.55 mmol) and potassium carbonate (K_2CO_3, 82.9 mg, 0.6 mmol) were added. The reaction mixture was stirred at room temperature for 4 hours. Dimethylformamide was distillated under reduced pressure, followed by extraction with ethylacetate (EtOAc). The extracted organic layer was dried over $MgSO_4$, filtered and concentrated. The concentrated reactant was separated by column chromatography (developing solvent: hexane/ethylacetate=15/1) to give 220 mg of the target compound (yield: 93%).

mp. 178-180° C.;

[1]H-NMR (300 MHz, DMSO-d[6]) δ 10.84 (s, 1H), 8.26 (s, 1H), 7.80 (s, 1H), 7.68 (d, J=2.73 Hz, 1H), 7.60 (dd, J=11.6 Hz, J=2.7 Hz, 1H), 7.47-7.48 (m, 2H), 7.30-7.34 (m, 4H), 5.23 (s, 2H).

EXAMPLE 59

Preparation of 5-chloro-2-hydroxy-N-phenylbenzamide



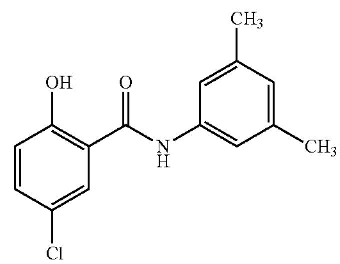
The target compound (yield: 16%) was obtained by the same manner as described in Example 1 except that aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

mp. 211-212° C.;

[1]H-NMR (300 MHz, DMSO-d[6]) δ 11.84 (s, 1H), 10.40 (s, 1H), 7.96 (d, J=2.6 Hz, 1H), 7.69 (d, J=8.3 Hz, 2H), 7.46 (dd, J=8.8 Hz, J=2.7 Hz, 1H), 7.34-7.39 (m, 2H), 7.15 (dd, J=7.2 Hz, J=7.2 Hz, 1H), 7.00 (d, J=8.8 Hz, 1H).

EXAMPLE 60

Preparation of 5-chloro-N-(3,5-dimethylphenyl)-2-hydroxybenzamide



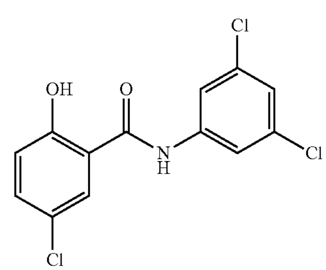
The target compound (yield: 22%) was obtained by the same manner as described in Example 1 except that 3,5-dimethylaniline was used instead of 3,5-bis(trifluoromethyl) aniline.

mp. 183-184° C.;

[1]H-NMR (300 MHz, DMSO-d[6]) δ 11.91 (s, 1H), 10.28 (s, 1H), 7.97 (d, J=2.6, 1H) 7.46 (dd, J=8.8 Hz, J=2.6 Hz, 1H), 7.32 (s, 2H), 7.00 (d, J=8.8 Hz, 1H), 6.79 (s, 1H), 2.49 (s, 6H).

EXAMPLE 61

Preparation of 5-chloro-N-(3,5-dichlorophenyl)-2-hydroxybenzamide



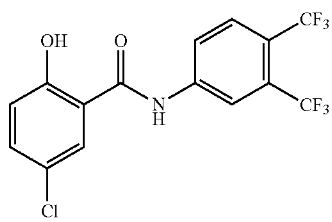
The target compound (yield: 24%) was obtained by the same manner as described in Example 1 except that 3,5-dichloroaniline was used instead of 3,5-bis(trifluoromethyl) aniline.

mp. 247-249° C.;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 11.44 (brs, 1H), 10.61 (s, 1H), 7.81-7.83 (m, 3H), 7.47 (dd, J=8.8 Hz, J=2.6 Hz, 1H), 7.36-7.37 (m, 1H), 7.02 (d, J=8.8 Hz, 1H).

EXAMPLE 62

Preparation of N-(3,4-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide



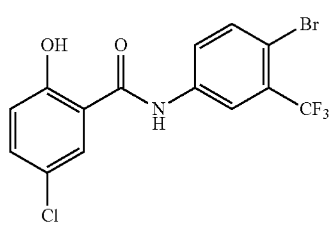
The target compound (yield: 5%) was obtained by the same manner as described in Example 1 except that 3,4-bis(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl) aniline.

mp. 215-217° C.;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14-8.16 (m, 2H), 7.97 (d, J=2.3 Hz, 1H), 7.84 (d, J=8.6 Hz, 1H), 7.38 (dd, J=8.8 Hz, J=2.3 Hz, 1H), 6.95 (d, J=8.8 Hz, 1H).

EXAMPLE 63

Preparation of N-(4-bromo-3-(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide



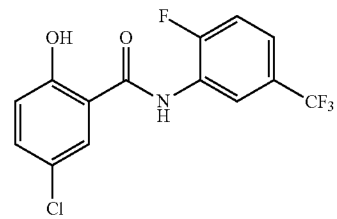
The target compound (yield: 26%) was obtained by the same manner as described in Example 1 except that 4-bromo-3-trifluoromethylaniline was used instead of 3,5-bis(trifluoromethyl)aniline.

mp. 238-240° C.;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 11.53 (brs, 1H), 10.65 (s, 1H), 8.29 (s, 1H), 7.85-7.93 (m, 3H), 7.44-7.48 (dd, J=8.8 Hz, J=2.6 Hz, 1H), 7.02 (d, J=8.8 Hz, 1H).

EXAMPLE 64

Preparation of 5-chloro-N-(2-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxybenzamide



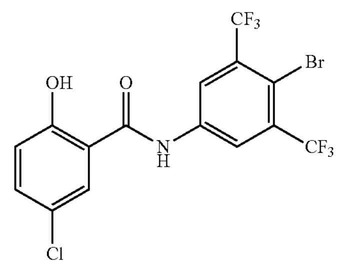
The target compound (yield: 38%) was obtained by the same manner as described in Example 1 except that 2-fluoro-5-trifluoromethylaniline was used instead of 3,5-bis(trifluoromethyl)aniline.

mp. 199-200;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 12.25 (brs, 1H), 10.91 (s, 1H), 8.72 (d, J=8.2 Hz, 1H), 7.94 (d, J=2.8 Hz, 1H), 7.59 (d, J=8.1 Hz, 2H), 7.51 (dd, J=9.3 Hz, J=2.8 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H).

EXAMPLE 65

Preparation of N-(4-bromo-3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide



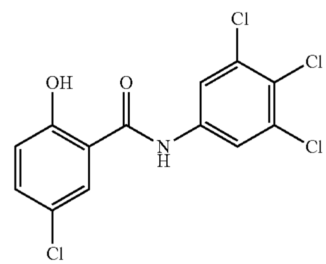
The target compound (yield: 20%) was obtained by the same manner as described in Example 1 except that 4-bromo-3,5-bis(trifluoromethyl)aniline was used instead of 3,5-bis(trifluoromethyl)aniline.

mp. 196-197;

^{1}H-NMR (300 MHz, DMSO-d^{6}) δ 10.91 (s, 1H), 8.55 (s, 2H), 7.83 (d, J=2.7, 1H), 7.49 (dd, J=8.7 Hz J=2.7 Hz, 1H), 7.03 (d, J=8.7 Hz, 1H).

EXAMPLE 66

Preparation of 5-chloro-2-hydroxy-N-(3,4,5-trichloro-phenyl)benzamide



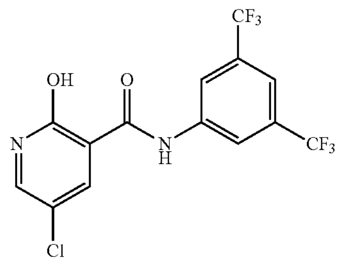
The target compound (yield: 44%) was obtained by the same manner as described in Example 1 except that 3,4,5-trichloroaniline was used instead of 3,5-bis(trifluoromethyl) aniline.

mp. 287-290;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 11.41 (brs, 1H), 10.68 (s, 1H), 8.05 (s, 2H), 7.81 (d, J=2.5 Hz, 1H), 7.47 (dd, J=8.7 Hz, J=2.5 Hz, 1H), 7.02 (d, J=8.8 Hz, 1H).

EXAMPLE 67

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxynicotineamide



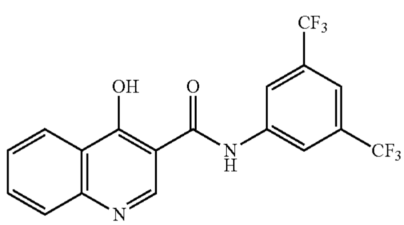
The target compound (yield: 49%) was obtained by the same manner as described in Example 1 except that 5-chloro-2-hydroxynicotinic acid was used instead of 5-chlorosalicylic acid.

mp. 333-335;

^{1}H-NMR (300 MHz, DMSO-d^6) δ 13.29 (brs, 1H), 12.46 (s, 1H), 8.37 (s, 2H), 8.34 (d, J=2.7 Hz, 1H), 8.13 (d, J=2.9 Hz, 1H), 7.79 (s, 1H).

EXAMPLE 68

Preparation of N-(3,5-bis(trifluoromethyl)phenyl)-4-hydroxyquinoline-3-carboxamide

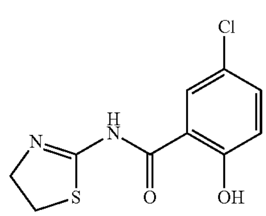


The target compound (yield: 10%) was obtained by the same manner as described in Example 1 except that 4-hydroxyquinoline-3-carboxylic acid was used instead of 5-chlorosalicylic acid.

^{1}H-NMR (300 MHz, DMSO-d^6) δ 11.47 (s, 1H), 9.11 (s, 1H), 8.40 (s, 2H), 8.37 (d, J=8.3 Hz, 1H), 8.20 (d, J=8.2 Hz, 1H), 8.00 (dd, J=7.2 Hz, J=7.2 Hz, 1H), 7.87-7.91 (m, 2H).

EXAMPLE 69

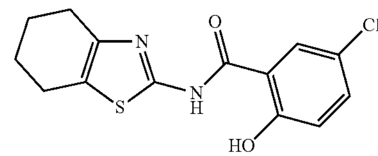
Preparation of 5-chloro-N-(4,5-dihydrothiazol-2-yl)-2-hydroxybenzamide



The target compound was purchased by Enamine (Enamine, Z68175643)

EXAMPLE 70

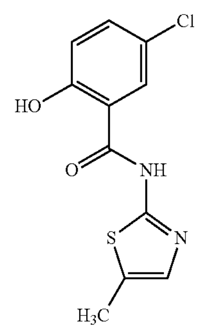
Preparation of 5-chloro-2-hydroxy-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide



The target compound was purchased by Enamine (Enamine, Z68484867)

EXAMPLE 71

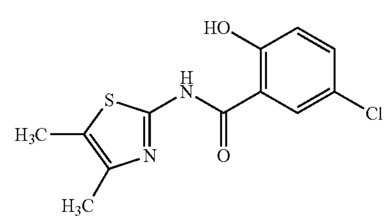
Preparation of 5-chloro-2-hydroxy-N-(5-methylthiazole-2-yl)benzamide



The target compound was purchased by Enamine (Enamine, Z68683800)

EXAMPLE 72

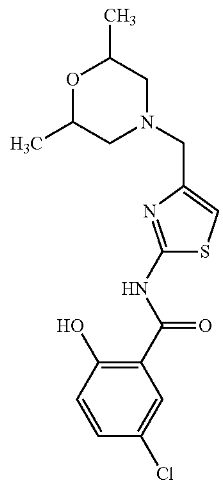
Preparation of 5-chloro-N-(4,5-dimethylthiazol-2-yl)-2-hydroxybenzamide



The target compound was purchased by Enamine (Enamine, Z203227614)

EXAMPLE 73

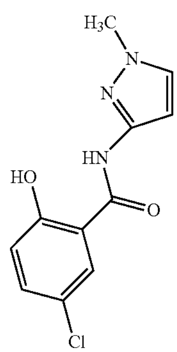
Preparation of 5-chloro-N-(4-((2,6-dimethylmorpholino)methyl)thiazol-2-yl)-2-hydroxybenzamide



The target compound was purchased by Enamine (Enamine, Z230310192)

EXAMPLE 74

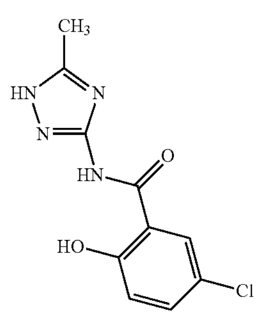
Preparation of 5-chloro-2-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide



The target compound was purchased by Enamine (Enamine, Z240293532)

EXAMPLE 75

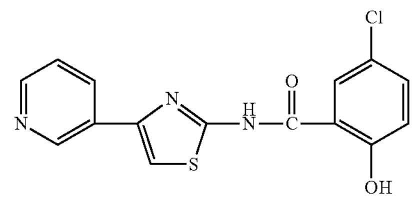
Preparation of 5-chloro-2-hydroxy-N-(5-methyl-1H-1,2,4-triazol-3-yl)benzamide



The target compound was purchased by Enamine (Enamine, Z1255527342)

EXAMPLE 76

Preparation of 5-chloro-2-hydroxy-N-(4-(pyridin-3-yl)thiazol-2-yl)benzamide



The target compound was purchased by Enamine (Enamine, Z68700988)

Experimental Example 1

Inhibitory Effect on TMPRSS4 Serine Protease Activity

The following experiment was performed to investigate the inhibitory effect of the compound of the present invention on the activity of TMPRSS4 serine protease expressed in cancer cells.

Step 1: Expression and Purification of TMPRSS4/MT-SP2 Serine Protease Domain

TMPRSS4 serine protease domain (205^{th} Val~437^{th} Leu) was cloned in pET21b/NdeI-XhoI, which was introduced in *E. coli* BL21 (DE3). At this time, FlagX2-enterokinase cleavage site (DYKDDDGDYKDDDDK; total 15 amino acids) was inserted in N-terminal of TMPRSS4 serine protease domain as shown in FIG. **1**. The forward and reverse primers for PCR used for the cloning were presented by SEQ. ID. NO: 1 and NO: 2.

The cells were cultured in 10 ml of LB containing ampicillin at 37° C. overnight. IL of LB+ampicillin was added thereto, followed by further culture until OD reached 0.6~0.8. 0.1 mM IPTG was added thereto, followed by further culture for 16 hours. Cell pellet was obtained, purified by Ni-NTA (Qiagen), and dialyzed. TMPRSS4 serine protease (proform) labeled with 2 mg of 2Xflag-enterokinase cleavage site was conjugated to Ni-NTA resin (4°, overnight). Enterokinase (NEB) was treated thereto at the concentration of 0.0002%/w/w at room temperature for 5 hours. The sample was washed, eluted with 50 mM imidazole in 20 mM of sodium phosphate buffer, and then dialyzed. As a result, active form of TMPRSS4 serine protease was obtained (FIG. **2**).

Step 2: Investigation of TMPRSS4 Serine Protease Activity Using Peptide Substrate

To investigate whether or not the purified TMPRSS4 serine protease active form had protease activity, the following experiment was performed using trypsin peptide substrate (Boc-Gln-Ala-Arg-7-amido-4-methylcoumarin hydrochloride; Sigma B4153) and kallikrein peptide substrate (Z-Phe-Arg 7-amido-4-methylcoumarin hydrochloride; Sigma C9521). The protein activity was evaluated by measuring fluorescence shown during hydrolysis of the peptide. As a result, the TMPRSS4 serine protease active form could hydrolyze the peptide substrate dose-dependently. It was also confirmed that such activity was inhibited by 1 mM of AEBSF (Sigma), the conventional serine protease inhibitor. TMPRSS4 pro-form (before digesting with enterokinase) did not show any activity, as expected, and trypsin (Try (0.04 μg)) was used as the control (FIG. **3** and FIG. **4**). Reaction was induced after adding 100 μM of the peptide substrate into reaction buffer (50 mM Tris-HCl (pH 8.0), 10 mM $CaCl_2$, 1 μM $ZnCl_2$). Then, fluorescence was measured at 5 minutes interval (excitation 385 nm, emission 455 nm).

The TMPRSS4 hydrolase activity of the compounds of Examples 1~68 was measured by the similar method to the above in order to evaluate the effect of the compounds: 2 μg of the TMPRSS4 serine protease active form and 100 μM kallikrein peptide substrate (Z-Phe-Arg7-amido-4-methylcoumarin hydrochloride; Sigma C9521) were mixed in reaction buffer (50 mM Tris-HCl (pH8.0), 10 mM $CaCl_2$, 1 μM $ZnCl_2$). Then, fluorescence (excitation 385 nm/emission 455 nm) was measured at 5 minutes interval for 150 minutes. At this time, after adding each compound of the present invention to the reaction buffer, reaction was induced and then the inhibitory effect of each compound on the TMPRSS4 serine protease activity was investigated. Dimethylsulfoxide (DMSO) was used as the negative control. The results are shown in Table 2.

TABLE 2

Formula	Intracellular protease activity Inhibition %		
	100 uM	30 uM	10 uM
Example 1	100	96	64
Example 2	N/D	100	100
Example 3	N/D	64	0
Example 4	98	86	64
Example 5	N/D	20	0
Example 6	99	88	67
Example 7	N/D	53	0
Example 8	N/D	96	58
Example 9	N/D	84	54
Example 10	N/D	91	37
Example 11	88	47	12
Example 12	69	29	N/D
Example 13	N/D	79	32
Example 14	N/D	55	0
Example 15	N/D	100	22
Example 16	98	93	80
Example 17	N/D	77	29
Example 18	N/D	54	46
Example 19	100	88	N/D
Example 20	N/D	100	40
Example 21	N/D	100	100
Example 22	100	100	64
Example 23	100	99	64
Example 24	N/D	63	36
Example 25	75	8	N/D
Example 26	N/D	93	61
Example 27	100	92	N/D
Example 28	100	75	N/D
Example 29	N/D	100	43
Example 30	N/D	31	5
Example 31	N/D	30	3
Example 32	99	95	71
Example 33	N/D	94	51
Example 34	N/D	78	33
Example 35	N/D	0	0
Example 36	N/D	98	53
Example 37	N/D	63	26
Example 38	N/D	21	0
Example 39	N/D	80	56
Example 40	11	0	N/D
Example 41	47	25	N/D
Example 42	55	14	N/D
Example 43	51	31	N/D
Example 44	18	8	N/D
Example 45	39	6	N/D
Example 46	0	0	N/D
Example 47	21	35	N/D
Example 48	0	0	N/D
Example 49	2	0	N/D
Example 50	67	0	N/D
Example 51	90	44	N/D

TABLE 2-continued

Formula	Intracellular protease activity Inhibition %		
	100 uM	30 uM	10 uM
Example 52	100	61	N/D
Example 53	98	91	N/D
Example 54	N/D	74	29
Example 55	N/D	78	33
Example 56	N/D	53	15
Example 57	N/D	4	0
Example 58	N/D	6	0
Example 59	75	13	N/D
Example 60	56	44	N/D
Example 61	N/D	58	15
Example 62	N/D	59	37
Example 63	98	46	30
Example 64	100	100	67
Example 65	N/D	85	58
Example 66	N/D	23	6
Example 67	N/D	19	0
Example 68	N/D	0	0
Example 69	N/D	N/D	17
Example 70	N/D	N/D	77
Example 71	N/D	N/D	66
Example 72	N/D	N/D	16
Example 73	N/D	N/D	85
Example 74	N/D	N/D	14
Example 75	N/D	N/D	58
Example 76	N/D	N/D	30

* N/D indicates No Data.

As shown in Table 2, it was confirmed that the compounds of Examples 1~76 of the present invention could inhibit the TMPRSS4 serine protease activity dose-dependently by the examination using peptide substrate. The TMPRSS4 serine protease activity was 47~100% inhibited by those compounds of Examples 1~4, 6~11, 13~24, 26~29, 32~34, 36, 37, 52~55, 61~63, 65, at the concentration of 30 μM. Particularly, the compounds of Examples 1, 2, 4, 6, 8, 9, 16, 21~23, 26, 32, 33, 36, 39, 65, 66, 70, 71, 73, 75 could inhibit the activity 51~100% at the concentration of 10 μM.

Therefore, the compounds of the present invention had excellent inhibitory effect on TMPRSS4 serine protease activity, suggesting that they could be effectively used as a composition for preventing or treating cancer by inhibiting TMPRSS4 over-expressed in cancer cells, particularly in lung cancer, colorectal cancer, and stomach cancer cells.

Experimental Example 2

Inhibitory Effect on Infiltration of Cancer Cells Over-Expressing TMPRSS4

The following experiment was performed to investigate the inhibitory effect of the compounds confirmed to have excellent effect of inhibiting TMPRSS4 serine protease activity in Experimental Example 1 on infiltration of cancer cells over-expressing TMPRSS4.

Step 1: Construction of Cancer Cell Line Over-Expressing TMPRSS4

Colorectal cancer cell line SW480 was mixed with 4 μg of pCMV-myc-TMPRSS4 expression vector (Korean Patent No. 10-0906145; Heekyung Jung, et al., *Oncogene,* 27(18), 2635-2647 (2008)) and 10 μl of lipofectamine (Invitrogen, USA) in 2.5 ml of Opti-MEM medium, followed by transfection according to the manufacturer's protocol (Invitrogen, USA). The cells were distributed in a 6-well plate at the density of 3×10^5 cells/well, followed by transfection. 48

hours later, the medium was replaced with a selection medium (800 μg/ml G418 medium). G418-resistant clone was separated, followed by culture for 2 weeks, during which selection was performed. As a result, TMPRSS4 over-expressing cell line was constructed.

Step 2: Effect on Cancer Cell Infiltration

The cancer cell line constructed in step 1 was distributed in a 24-well trans-well plate (8 μm pore size; Costar, USA) whose porous membrane was coated with 100 μl of matrigel (BD Biosciences, USA) diluted with serum-free medium at the concentration of 250 μg/ml, which stood at room temperature for 1 hour for solidification. Lower chamber of the trans-well plate was coated with 100 μl of collagen type I (Sigma) at the concentration of 20 μg/ml. 4×10^4 cells resuspended in the serum-free medium containing the compounds of Examples 1~68 of the present invention were distributed in the upper chamber. The serum-free medium containing the compounds of the present invention was distributed in the lower chamber. While culturing the cells in a 37, 5% CO_2 incubator for 48 hours, cell migration from the upper chamber to lower chamber was allowed. Those cells that did not migrate were eliminated from the surface of the upper chamber. The cells migrated from the upper chamber to the lower chamber were fixed in 3.7% paraformaldehyde dissolved in PBS, followed by staining with 2% crystal violet solution. The excessive crystal violet solution was washed away with distilled water. The migrated cell number was counted from 5 randomly selected areas (×200). The experiment was repeated at least twice under the same condition, and the representative result was presented.

The inhibitory effect of each compound on the infiltration of TMPRSS4 over-expressing colorectal cancer cell line SW480 was calculated by Mathematical Formula 1, which presents the number of infiltrated cells with % by the number of infiltrated cells in the negative control treated with DMSO. The results are shown in Table 3.

Infiltration Inhibition Rate (%)=100−Infiltrated cell number with the treatment of each compound/Infiltrated cell number with the treatment of DMSO×100 [Mathematical Formula 1]

TABLE 3

Formula	Inhibition rate of target-expressing colorectal cancer cell activity (%, 0.1~2 uM)
Example 1	76 (0.8 uM)
Example 6	49 (0.8 uM)
Example 8	72 (0.8 uM)
Example 19	81 (2 uM)
Example 22	43 (0.1 uM)
Example 25	51 (25 uM)
Example 27	54 (2 uM)
Example 28	52 (2 uM)
Example 32	68 (0.8 uM)
Example 33	43 (0.1 uM)
Example 36	76 (0.8 uM)
Example 37	44 (5 uM)
Example 53	34 (0.1 uM), 56 (1 uM)
Example 55	26 (0.1 uM)
Example 65	53 (0.1 uM)

As shown in Table 3, the compounds of Examples 1, 6, 8, 19, 22, 25, 27, 28, 32, 33, 36, 37, 53, 55 and 65 were confirmed to inhibit the infiltration of colorectal cancer cells expressing TMPRSS4 26~81%. The compounds of Examples 1, 8, 19, 25, 27, 28, 32, 36, 53 and 65 inhibited the infiltration 51~81%. In particular, the compound of Example 19 inhibited the infiltration 81%.

Therefore, the compounds of the present invention had excellent effect of inhibiting the infiltration of cancer cells expressing TMPRSS4, suggesting that they could be effectively used as a composition for preventing or treating cancer owing to their excellent effect of inhibiting cancer cell infiltration.

SEQUENCE LISTING

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What is claimed is:

1. A method for inhibiting colorectal cancer metastasis comprising: administrating a pharmaceutically effective dose of a 2-hydroxyarylamide derivative or a pharmaceutically acceptable salt thereof, wherein the 2-hydroxyarylamide derivative is selected from the group consisting of:

(6) 5-chloro-2-hydroxy-N-(3-methoxy-5-(trifluoromethyl)phenyl)benzamide;

(19) 5-chloro-N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(25) 5-chloro-2-hydroxy-N-quinoline-3-yl-benzamide;

(27) 5-chloro-N-(2-chloro-4-cyano-phenyl)-2-hydroxy-benzamide;

(28) 5-chloro-2-hydroxy-N-(5-trifluoromethyl-[1,3,4]thiadiazole-2-yl)-benzamide;

(32) 5-chloro-N-(4-chloro-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide;

(36) 5-chloro-2-hydroxy-N-(2-nitro-4-trifluoromethyl-phenyl)-benzamide;

(37) 5-chloro-N-(5-cyano-pyridine-2-yl)-2-hydroxy-benzamide; and

(53) 5-chloro-2-hydroxy-N-(4-phenylthiazole-2-yl)benzamide;

wherein the 2-hydroxyarylamide derivative or a pharmaceutically acceptable salt thereof inhibits the activity of TMPRSS4 (transmembrane protease serine-4).

2. The method of claim 1, wherein the 2-hydroxyarylamide derivative or a pharmaceutically acceptable salt thereof is administered orally or parenterally.

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